JULY 2000
VOLUME 45
NUMBER 7
ISSN 0020-1324-RECACP

www.rcjournal.com

RESPIRATORY CARE

A MONTHLY SCIENCE JOURNAL
44TH YEAR—ESTABLISHED 1956

AARC

46th International Respiratory Congress
October 7-10 • Cincinnati, Ohio

NOW IN Index Medicus/MEDLINE

EDITORIALS

Bronchodilation in Mechanically Ventilated Patients

ORIGINAL CONTRIBUTIONS

Bronchodilator Therapy with Metered-Dose Inhaler and Spacer versus Nebulizer in Mechanically Ventilated Patients

THE NEW HORIZONS SYMPOSIUM PAPERS

Foreword: The Pharmacology of Inhaled Aerosol Drug Therapy

Pharmacokinetics and Pharmacodynamics of Drugs Administered by Aerosol

Inhalable Drugs for Systemic Therapy

Inhaled Antimicrobial Therapy

Inhaled Corticosteroids

Inhaled Adrenergic Bronchodilators

Inhaled Anticholinergic Therapy

Mucoactive Aerosol Therapy

Aerosol Device Selection

Introducing the low-volume surfactant.*

Curosurf has established itself as the #1 selling surfactant in Europe[1] and has saved thousands of infants born with RDS since 1992. Now, it's available in the United States.

Curosurf permits you to reduce the volume of administration 37% (initial dose) and 68% (repeat dose) compared to Survanta® (beractant) and 12% (initial dose) and 55% (repeat dose) compared to Infasurf® (calfactant).*

Curosurf permits fewer dosing positions and a longer interval between doses (12 hours) than the market leader.[2]* For administration, brief disconnection of the endotracheal tube from the ventilator is required.

Infants receiving Curosurf should receive frequent clinical and laboratory assessments so that oxygen and ventilator support can be modified to respond to respiratory changes.

Transient adverse effects seen with the administration of Curosurf include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation.

Curosurf is conveniently available in two vial sizes (1.5 mL and 3.0 mL).

We'd like to share the whole clinical story with you. Please call us at 800-755-5560 or visit us at our Web site www.deyinc.com

***Clinical studies have not evaluated if low volume or convenience features result in superior safety or efficacy on clinically relevant endpoints.**

New for RDS!

Curosurf®
(poractant alfa)
Intratracheal Suspension

DEY

DEY 2751 Napa Valley Corporate Drive Napa, CA 94558 Please see brief prescribing information on adjacent page.

Circle 138 on product info card

New for RDS!

Curosurf®
(poractant alfa)
Intratracheal Suspension

NDC Number	Description	Concentration (mg/mL)	mL/Vial	Units Per Carton
49502-180-01	Curosurf	80	1.5	1
49502-180-03	Curosurf	80	3	1

CUROSURF®
(poractant alfa)

INTRATRACHEAL SUSPENSION
Brief Summary: Please see full package insert for full prescribing information.

INDICATION AND USAGE
CUROSURF is indicated for the treatment (rescue) of Respiratory Distress Syndrome (RDS) in premature infants. CUROSURF reduces mortality and pneumothoraces associated with RDS.

CLINICAL STUDIES
The clinical efficacy of CUROSURF was demonstrated in one single-dose study (Study 1) and one multiple-dose study (Study 2) in the treatment of established neonatal RDS involving approximately 500 infants. Each study was randomized, multicenter, and controlled. REFER TO PACKAGE INSERT FOR STUDY DESCRIPTION RESULTS.

ACUTE CLINICAL EFFECTS
As with other surfactants, marked improvements in oxygenation may occur within minutes of the administration of CUROSURF.

WARNINGS
CUROSURF is intended for intratracheal use only.

THE ADMINISTRATION OF EXOGENOUS SURFACTANTS, INCLUDING CUROSURF, CAN RAPIDLY AFFECT OXYGENATION AND LUNG COMPLIANCE. Therefore, infants receiving CUROSURF should receive frequent clinical and laboratory assessments so that oxygen and ventilatory support can be modified to respond to respiratory changes. CUROSURF should only be administered by those trained and experienced in the care, resuscitation, and stabilization of pre-term infants.

TRANSIENT ADVERSE EFFECTS SEEN WITH THE ADMINISTRATION OF CUROSURF INCLUDE BRADYCARDIA, HYPOTENSION, ENDOTRACHEAL TUBE BLOCKAGE, AND OXYGEN DESATURATION. These events require stopping Curosurf administration and taking appropriate measures to alleviate the condition. After the patient is stable, dosing may proceed with appropriate monitoring.

PRECAUTIONS
General
Correction of acidosis, hypotension, anemia, hypoglycemia, and hypothermia is recommended prior to CUROSURF administration.

Surfactant administration can be expected to reduce the severity of RDS but will not eliminate the mortality and morbidity associated with other complications of prematurity.

Sufficient information is not available on the effects of administering initial doses of CUROSURF other than 2.5 mL/kg (200 mg/kg), subsequent doses other than 1.25 mL/kg (100 mg/kg), administration of more than three total doses, dosing more frequently than every 12 hours, or initiating therapy with CUROSURF more than 15 hours after diagnosing RDS. Adequate data are not available on the use of CUROSURF in conjunction with experimental therapies of RDS, e.g., high-frequency ventilation.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY
Studies to assess potential carcinogenic and reproductive effects of CUROSURF, or other surfactants, have not been conducted.

Mutagenicity studies of CUROSURF, which included the Ames test, gene mutation assay in Chinese hamster V79 cells, chromosomal aberration assay in Chinese hamster ovarian cells, unscheduled DNA synthesis in HELA S3 cells, and *in vivo* mouse nuclear test, were negative.

ADVERSE REACTIONS
Transient adverse effects seen with the administration of CUROSURF include bradycardia, hypotension, endotracheal tube blockage, and oxygen desaturation.

The rates of common complications of prematurity observed in Study 1 are shown below in Table 3.

TABLE 3
COMPLICATIONS OF PREMATURITY

	CUROSURF 2.5 mL/kg (200 mg/kg) n=78 %	CONTROL* n=66 %
Acquired Pneumonia	17	21
Acquired Septicemia	14	18
Bronchopulmonary Dysplasia	18	22
Intracranial Hemorrhage	51	64
Patent Ductus Arteriosus	60	48
Pneumothorax	21	36
Pulmonary Interstitial Emphysema	21	38

*Control patients were disconnected from the ventilator and manually ventilated for 2 minutes. No surfactant was instilled.

Immunological studies have not demonstrated differences in levels of surfactant-anti-surfactant immune complexes and anti-CUROSURF antibodies between patients treated with CUROSURF and patients who received control treatment.

OVERDOSAGE
There have been no reports of overdosage following the administration of CUROSURF.

In the event of accidental overdosage, and only if there are clear clinical effects on the infant's respiration, ventilation, or oxygenation, as much of the suspension as possible should be aspirated and the infant should be managed with supportive treatment, with particular attention to fluid and electrolyte balance.

Dosing Precautions
Transient episodes of bradycardia, decreased oxygen saturation, reflux of the surfactant into the endotracheal tube, and airway obstruction have occurred during the dosing procedure of CUROSURF. These events require interrupting the administration of CUROSURF and taking the appropriate measures to alleviate the condition. After stabilization, dosing may resume with appropriate monitoring.

HOW SUPPLIED
CUROSURF® (poractant alfa) Intratracheal Suspension (NDC Numbers: 49502-180-01 [1.5 mL]; 49502-180-03 [3 mL]) is available in sterile, ready-to-use rubber-stoppered clear glass vials containing 1.5 mL (120 mg phospholipids) or 3 mL (240 mg phospholipids) of suspension. One vial per carton.

Rx only.

DEY

Manufactured for DEY by
Chiesi Farmaceutici, S.p.A.
26/A Via Palermo & 96 Via San Leonardo
Parma, Italy 43100

03-572-00(BRS) 2/00

1. IMS Retail and Provider Perspective 2/00. 2. Refer to Survanta® prescribing information.
Survanta® is a registered trademark of Ross Products Division. Infasurf® is a registered trademark of Forest Pharmaceuticals, Inc.

©2000 DEY®
09-772-00 2/00

Twenty years in the making.
An overnight success.

Bio-logic brings twenty years of electrodiagnostic expertise and ten years of leadership in sleep diagnostics to introduce new Sleepscan II, the leading edge in Windows®-based digital polysomnography.

- Fully digital amplifiers create crystal clear signals.
- Expert analysis modules let your lab customize event scoring and editing.
- New, patented SmartPack™ data compression optimizes sampling rates and file management.

New Sleepscan II.
The overnight success story.

SLEEPSCAN™ II

1-800-323-8326 ext. 700
www.bio-logic.com

Bio-logic SYSTEMS CORP

INNOVATION THAT MAKES A DIFFERENCE

Circle 125 on product info card

CONTENTS

JULY 2000 / VOLUME 45 / NUMBER 7

FOR INFORMATION, CONTACT:

AARC Membership or Other AARC Services
American Association for Respiratory Care
11030 Ables Ln
Dallas TX 75229-4593
(972) 243-2272 • Fax (972) 484-2720
http://www.aarc.org

Therapist Registration or Technician Certification
National Board for Respiratory Care
8310 Nieman Rd
Lenexa KS 66214
(913) 599-4200 • Fax (913) 541-0156
http://www.nbrc.org

Accreditation of Education Programs
Committee on Accreditation for Respiratory Care
1701 W Euless Blvd, Suite 300
Euless TX 76040
(817) 283-2835 • Fax (817) 354-8519
http://www.coarc.com

Grants, Scholarships, Community Projects
American Respiratory Care Foundation
11030 Ables Ln
Dallas TX 75229-4593
(972) 243-2272 • Fax (972) 484-2720

AARC Government Affairs Office
Director of Govt Affairs
Jill Eicher
1225 King St, Second Floor
Alexandria VA 22314
(703) 548-8538 Fax (703) 548-8499
eicher@aarc.org

Director of State Govt Affairs
Cheryl West MHA
8630 Braeswood Pt. #2
Colorado Springs, CO 80920
(719) 535-9970 west@aarc.org

RESPIRATORY CARE

RESPIRATORY CARE (ISSN 0020-1324, USPS 0489-190) is published monthly by Daedalus Enterprises Inc, at 11030 Ables Lane, Dallas TX 75229-4593, for the American Association for Respiratory Care. One volume is published per year beginning each January. Subscription rates are $75 per year in the US; $90 in all other countries (for airmail, add $94).

The contents of the Journal are indexed in Hospital and Health Administration Index, Cumulative Index to Nursing and Allied Health Literature, EMBASE/Exerpta Medica, and RNdex Library Edition. Abridged versions of RESPIRATORY CARE are also published in Italian, French, and Japanese, with permission from Daedalus Enterprises Inc.

Periodicals postage paid at Dallas TX and at additional mailing offices. POSTMASTER: Send address changes to RESPIRATORY CARE, Membership Office, Daedalus Enterprises Inc, 11030 Ables Lane, Dallas TX 75229-4593.

♻Printed on acid-free paper.
Printed in the United States of America
Copyright © 2000, by Daedalus Enterprises Inc.

EDITORIALS

Bronchodilation in Mechanically Ventilated Patients: How Much Is Enough and How Best to Deliver?
by Constantine A Manthous—Bridgeport, Connecticut **815**

ORIGINAL CONTRIBUTIONS

Bronchodilator Therapy with Metered-Dose Inhaler and Spacer Versus Nebulizer in Mechanically Ventilated Patients: Comparison of Magnitude and Duration of Response
by Alexander G Duarte, Keith Momii, and Akhil Bidani—Galveston, Texas **817**

THE NEW HORIZONS SYMPOSIUM: INHALED AEROSOL DRUG THERAPY

GUEST CO-CHAIRS

James B Fink MS RRT FAARC and
Joseph L Rau PhD RRT FAARC

FOREWORD

New Horizons in Respiratory Care: The Pharmacology of Inhaled Aerosol Drug Therapy
by James B Fink—Sunnyvale, California and Joseph L Rau—Atlanta, Georgia **824**

SYMPOSIUM PAPERS

The Fate of Inhaled Drugs: The Pharmacokinetics and Pharmacodynamics of Drugs Administered by Aerosol
by Theodore J Witek Jr—Ridgefield, Connecticut **826**

Inhalable Drugs for Systemic Therapy
by Kevin Corkery—San Carlos, California **831**

Inhaled Antimicrobial Therapy: From Cystic Fibrosis to the Flu
by Thomas G O'Riordan—Stony Brook, New York **836**

Comparing Inhaled Corticosteroids
by Gene L Colice—Washington, DC **846**

Inhaled Adrenergic Bronchodilators: Historical Development and Clinical Application
by Joseph L Rau—Atlanta, Georgia **854**

Clinical Aspects of Inhaled Anticholinergic Therapy
by Sammy C Campbell—Tucson, Arizona **864**

Evaluating the Efficacy of Mucoactive Aerosol Therapy
by Mamta Fuloria and Bruce K Rubin—Winston-Salem, North Carolina **868**

Aerosol Device Selection: Evidence to Practice
by James B Fink—Sunnyvale, California **874**

The Gold Standard just got better...

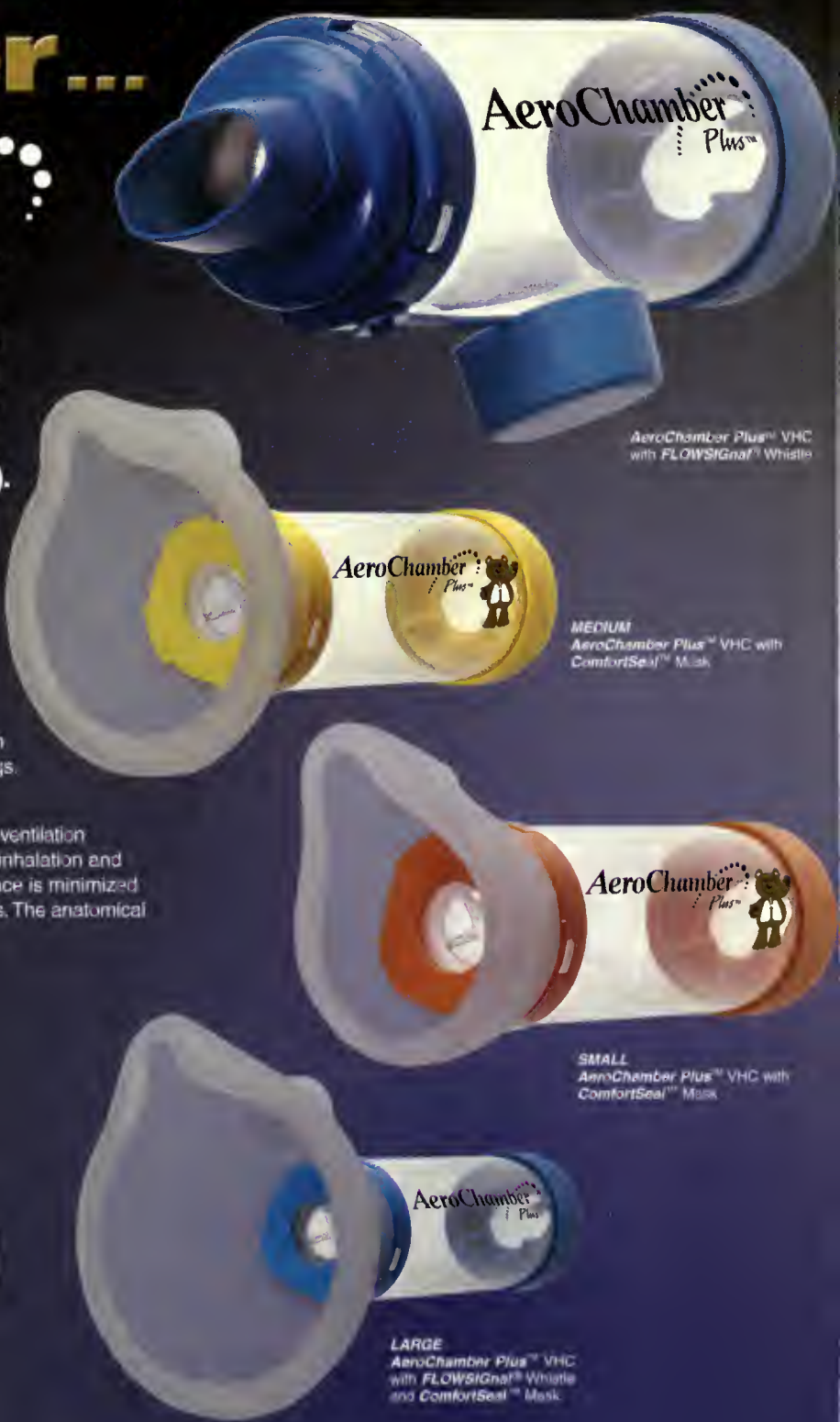
AeroChamber Plus™

Continuing with the tradition of innovation – Monaghan Medical is proud to introduce the newly designed *AeroChamber Plus*™ Valved Holding Chamber ("VHC").

Improved aerodynamic body.
Delivering medication is serious business. Monaghan Medical's new design of the ***AeroChamber Plus***™ VHC delivers more aerosol particles to your patient's respiratory system.

New valve and baffle system.
The industry standard has been redefined to deliver more medication more efficiently. Our new valve system allows flow in one direction only – to your patient's lungs.

Completely redesigned mask.
A reliable seal is critical for aerosol delivery and efficient ventilation with children. Our new masks provide low resistance inhalation and exhalation with the new tamper proof valve. Dead space is minimized with the comfortable fit of our soft 100% silicone masks. The anatomical designs fit children from infant to toddler and older.


AeroChamber Plus™
AeroChamber Plus™ VHC with FLOWSIGnal® Whistle
MEDIUM
AeroChamber Plus™ VHC with ComfortSeal™ Mask
SMALL
AeroChamber Plus™ VHC with ComfortSeal™ Mask
LARGE
AeroChamber Plus™ VHC with FLOWSIGnal® Whistle and ComfortSeal™ Mask

AARC ZENITH AWARD 1999

monaghan

Monaghan Medical Corporation
PO Box 2805 • Plattsburgh, NY 12901-0299
Customer Service 800-833-9653
©1999 Monaghan Medical Corporation.
All rights reserved.

Circle 133 on product info card

CONTENTS

CONTINUED...

ALSO IN THIS ISSUE

895	AARC Membership Application
800	Abstracts from Other Journals
904	Advertisers Index & Help Lines
904	Author Index
894	Calendar of Events
899	Manuscript Preparation Guide
897	MedWatch
893	New Products
903	Notices

BOOKS, FILMS, TAPES, & SOFTWARE

Anticholinergic Agents in the Upper and Lower Airways (Spector SL, editor) **886**
reviewed by Donald W Cockcroft—Saskatoon, Saskatchewan, Canada

Exercise-Induced Asthma (McFadden ER, editor) **886**
reviewed by Joseph D Spahn—Denver, Colorado

Oxford Textbook of Critical Care (Webb AR, Shapiro MJ, Singer M, Suter PM, editors) **887**
reviewed by Benjamin D Medoff—Boston, Massachusetts

Atlas of Sleep Medicine in Infants and Children (Sheldon SH, Riter S, Detrojan M) **888**
reviewed by Lee J Brooks—Camden, New Jersey

RC WEB SITES

LifeMasters Online **890**
reviewed by Steven B Nelson—Rochester, Minnesota

Respiratory Product News **891**
reviewed by Steven B Nelson—Rochester, Minnesota

RESPIRATORY CARE

A Monthly Science Journal
Established in 1956

The Official Journal of the
American Association for
Respiratory Care

If you are looking for a ventilator that has...

VALUE

Your cost of ownership – from the initial investment to life-long maintenance – is surprisingly low with the E100M. And we back the E100M with our "No Risk, No Questions Asked 90 Day Money Back Guarantee."

VERSATILITY

Designed for neonates, pediatrics and adults, the E100M can be used throughout the hospital, in the ER, for intra-hospital transport and for subacute/long term care facilities – it goes where you need it.

PERFORMANCE

With comprehensive features such as pressure or volume ventilation, PEEP/CPAP, back-up ventilation and an 8 hour battery, the E100M performs beyond its compact profile.

RELIABILITY

Engineered for quality, durability and long life, the E100M is the ventilator you can count on.

You've found it... the Newport E100M. Give it a try, it just may be the ventilator you've been looking for. But if it's not all we say it is, then we will refund your investment.

We stand behind our products and behind our "No Risk, No Questions Asked 90 Day Money Back Guarantee." Contact us today. The E100M is here now.

NEWPORT NMI

Moving in all the right directions.℠

800.451.3111 1.949.642.3910

www.NewportNMI.com

Circle 118 on reader service card

EDITORIAL OFFICE

600 Ninth Avenue, Suite 702
Seattle WA 98104
(206) 223-0558
Fax (206) 223-0563
www.rcjournal.com

MANAGING EDITOR

Ray Masferrer RRT

ASSISTANT EDITOR

Katherine Kreilkamp

EDITORIAL ASSISTANT

Linda Barcus

COPY EDITOR

Matthew Mero

PRODUCTION

Kelly Piotrowski

PUBLISHER

Sam P Giordano MBA
RRT FAARC

MARKETING

Dale L Griffiths
Director of Marketing

Tim Goldsbury
Director, Advertising Soles

Beth Binkley
Advertising Assistant

RESPIRATORY CARE

A Monthly Science Journal
Established in 1956

The Official Journal of the
American Association for
Respiratory Care

EDITOR IN CHIEF

David J Pierson MD FAARC
Harborview Medical Center
University of Washington
Seattle, Washington

ASSOCIATE EDITORS

Richard D Branson RRT
University of Cincinnati
Cincinnati, Ohio

Charles G Durbin Jr MD
University of Virginia
Charlottesville, Virginia

Dean R Hess PhD RRT FAARC
Massachusetts General Hospital
Harvard University
Boston, Massachusetts

James K Stoller MD
The Cleveland Clinic Foundation
Cleveland, Ohio

EDITORIAL BOARD

Alexander B Adams MPH RRT
Regions Hospital
St Paul, Minnesota

Thomas A Barnes EdD RRT FAARC
Northeastern University
Boston, Massachusetts

Michael J Bishop MD
University of Washington
Seattle, Washington

Bartolome R Celli MD
Tufts University
Boston, Massachusetts

Robert L Chatburn RRT FAARC
University Hospitals of Cleveland
Case Western Reserve University
Cleveland, Ohio

James B Fink MS RRT FAARC
Hines VA Hospital
Loyola University
Chicago, Illinois

Luciano Gattinoni MD
University of Milan
Milan, Italy

John E Heffner MD
Medical University of South Carolina
Charleston, South Carolina

Mark J Heulitt MD
University of Arkansas
Little Rock, Arkansas

Leonard D Hudson MD
University of Washington
Seattle, Washington

Robert M Kacmarek PhD RRT FAARC
Massachusetts General Hospital
Harvard University
Boston, Massachusetts

Toshihiko Koga MD
Koga Hospital
Kurume, Japan

Marin H Kollef MD
Washington University
St Louis, Missouri

Patrick Leger MD
Clinique Médicale Edouard Rist
Paris, France

Neil R MacIntyre MD FAARC
Duke University
Durham, North Carolina

John J Marini MD
University of Minnesota
St Paul, Minnesota

Shelley C Mishoe PhD RRT FAARC
Medical College of Georgia
Augusta, Georgia

Marcy F Petrini PhD
University of Mississippi
Jackson, Mississippi

Joseph L Rau PhD RRT FAARC
Georgia State University
Atlanta, Georgia

Catherine SH Sassoon MD
University of California Irvine
Long Beach, California

John W Shigeoka MD
Veterans Administration Medical Center
Salt Lake City, Utah

Arthur S Slutsky MD
University of Toronto
Toronto, Ontario, Canada

Martin J Tobin MD
Loyola University
Chicago, Illinois

Jeffrey J Ward MEd RRT
Mayo Medical School
Rochester, Minnesota

Robert L Wilkins PhD RRT
Loma Linda University
Loma Linda, California

STATISTICAL CONSULTANT

Gordon D Rubenfeld MD
University of Washington
Seattle, Washington

SECTION EDITORS

Hugh S Mathewson MD
Joseph L Rau PhD RRT FAARC
Drug Capsule

Charles G Irvin PhD
Gregg L Ruppel MEd RRT RPFT FAARC
PFT Corner

Richard D Branson RRT
Robert S Campbell RRT FAARC
Kittredge's Corner

Jon Nilsestuen PhD RRT FAARC
Ken Hargett RRT
Graphics Corner

Patricia Ann Doorley MS RRT
Charles G Durbin Jr MD
Test Your Radiologic Skill

Editorials, Commentaries, and Reviews To Note

Non-Invasive Ventilation in Acute Hypoxemic Respiratory Failure—Miletin MS, Detsky AS, Lapinsky SE, Mehta S. Intensive Care Med 2000 Feb;26(2):242–245.

Biological Effects of Hypercapnia—Laffey JG, Kavanagh BP. Intensive Care Med 2000 Jan; 26(1):133–138.

PRO: Noninvasive Ventilation Has Been Shown to Be Ineffective in Stable COPD (editorial)—Hill NS. Am J Respir Crit Care Med 2000 Mar;161(3 Pt 1):689–690; discussion 691.

CON: Noninvasive Ventilation Has Not Been Shown to Be Ineffective in Stable COPD (editorial)—Rossi A. Am J Respir Crit Care Med 2000 Mar;161(3 Pt 1):688–689.

Cardiopulmonary Resuscitation: Strengthening the Links in the Chain of Survival (editorial)—Ewy GA. N Engl J Med 2000 May 25;342(21):1599–1601.

Reversal of Intraoperative Myocardial Ischemia with a Hemoglobin-Based Oxygen Carrier—Niquille M, Touzet M, Leblanc I, Baron JF. Anesthesiology 2000 Mar;92(3):882–885.

Successful Use of Hypnosis As an Adjunctive Therapy for Weaning from Mechanical Ventilation—Treggiari-Venzi MM, Suter PM, de Tonnac N, Romand JA. Anesthesiology 2000 Mar;92(3):890–892.

How Molecular Epidemiology Has Changed What We Know about Tuberculosis (review)—Kato-Maeda M, Small PM. West J Med 2000 Apr;172(4):256–259.

How to Treat Influenza and Colds—Kim MC, Lee NP. West J Med 2000 Apr;172(4):260–264.

Additional Techniques for Managing the Difficult Pediatric Airway—Auden SM. Anesth Analg 2000 Apr;90(4):878–880.

Removal of an Aspirated Prosthetic Tooth by Tracheal Backflow Air—Fung ST, Poon YY, Chong ZK, Jawan B, Lee JH. Anesth Analg 2000 Apr;90(4):993–994.

Current Clinical Options for the Treatment and Management of Acute Respiratory Distress Syndrome (review)—Bulger EM, Jurkovich GJ, Gentilello LM, Maier RV. J Trauma 2000 Mar;48(3):562–572.

Evaluation of Tracheal Intubation Difficulty in Patients with Cervical Spine Immobilization: Fiberoptic (WuScope) Versus Conventional Laryngoscopy—Smith CE, Pinchak AB, Sidhu TS, Radesic BP, Pinchak AC, Hagen JF. Anesthesiology 1999 Nov;91(5):1253–1259.

BACKGROUND: The WuScope is a rigid, fiberoptic laryngoscope designed to facilitate tracheal intubation without the need for head extension. The study evaluated the WuScope in anesthetized patients with neck immobilization. METHODS: Patients were randomized to one of two groups: those receiving fiberoptic laryngoscopy (WuScope, n = 43) and those receiving conventional laryngoscopy (Macintosh blade, n = 44). Manual in-line stablization of the cervical spine was done during intubation. Seven parameters of intubation difficulty were measured (providing an intubation difficulty scale score): number of operators, number of attempts, number of techniques, Cormack view, lifting force, laryngeal pressure, and vocal cord position. RESULTS: Successful intubation occurred in 95% of patients in the fiberoptic group and in 93% of patients in the conventional group. There were no differences in number of attempts. In the fiberoptic group, 79% of patients had an intubation difficulty scale score of 0, representing an ideal intubation: that is, one performed by the first operator on the first attempt using the first technique with full glottic visualization. Only 18% of patients in the conventional group had an intubation difficulty scale score of 0 ($p < 0.001$). More patients had Cormack grade 3 or 4 views with conventional than with fiberoptic laryngoscopy (39 vs. 2%, $p < 0.001$). Intubation times in patients with one attempt were slightly longer in the fiberoptic (median, 25th-75th percentiles: 30, 23–53 s) compared with the conventional group (24, 17–30 s, $p < 0.05$). Corresponding times in patients requiring > one attempt were 155 (range, 112–201) s and 141 (range, 95–186) s in the fiberoptic and conventional groups, respectively (p value not significant).

CONCLUSIONS: Compared with conventional laryngoscopy, tracheal intubation using the fiberoptic laryngoscope was associated with lower intubation difficulty scale scores and better views of the laryngeal aperture in patients with cervical immobilization. However, there were no differences in success rates or number of intubation attempts.

Comparison of NAD 6000 and Servo 900C Ventilators in an Infant Lung Model—Stayer SA, Bent ST, Campos CJ, Skjonsby BS, Andropoulos DB. Anesth Analg 2000 Feb;90(2):315–321.

We compared the ability of the NAD 6000 (North American Dräger, Telford, PA) and the Servo 900C (Siemens-Elema AB, Solna, Sweden) anesthesia ventilators to maintain precise delivery of small tidal volumes (V_T) and positive end-expiratory pressure using an infant test lung model. A variety of ventilator and lung model settings were selected to test clinical conditions simulating normal and extremely compromised lung function. Differences in ventilator output were analyzed by using an independent t-test with $p < 0.05$ considered significant. With the ventilators set to deliver a V_T of 30 mL, the actual delivered V_T was significantly better for the NAD 6000 (25 ± 2 mL) compared with the Servo 900C (18 ± 3 mL), $p < 0.001$. When the ventilators were set to deliver 100 mL V_T, their delivered V_T were not significantly different, NAD 6000 (66 ± 19 mL) and Servo 900C (60 ± 12 mL), $p = 0.09$. The exhaled V_T read by the anesthesia machines was significantly closer to the delivered V_T for the NAD 6000 (11 ± 9 mL) compared with the Servo 900C (37 ± 11 mL), $p < 0.001$. Both ventilators maintained the end expiratory pressure delivered to the test lung within 2 cm H_2O of the set positive end-expiratory pressure on average. As the conditions changed requiring the ventilator to develop a higher peak inflating pressure, both ventilators showed a decrease in V_T delivered, which was proportionate to the tubing compression volume loss. IMPLICATIONS: The NAD 6000 (North American Dräger, Telford, PA) and Servo 900C (Siemens-Elema AB, Solna, Sweden) are able to precisely deliver small tidal volumes. They both decreased in performance when tested under extreme conditions. Earlier studies of traditional anesthesia ventilators suggest that the NAD 6000 and Servo 900C are superior pediatric ventilators.

Inhaled Nitric Oxide Delivery by Anesthesia Machines—Ceccarelli P, Bigatello LM, Hess D, Kwo J, Melendez L. Anesth Analg 2000 Feb; 90(2):482–488.

Inhaled nitric oxide (NO) is a selective pulmonary vasodilator used to treat intraoperative pulmonary hypertension and hypoxemia. In contrast to NO delivered by critical care ventilators, NO delivered by anesthesia machines can be complicated by rebreathing. We evaluated two methods of administering NO intraoperatively: via the nitrous oxide (N_2O) flowmeter and via the INOvent (Datex-Ohmeda, Madison, WI). We hypothesized that both systems would deliver NO accurately when the fresh gas flow (FGF) rate was higher than the minute ventilation ($\dot{V}_E$). Each system was set to deliver NO to a lung model. Rebreathing of NO was obtained by decreasing FGF and by simulating partial NO uptake by the lung. At FGF $\geq \dot{V}_E$ (6 L/min), both systems delivered an inspired NO concentration ([NO]) within approximately 10% of the [NO] set. At FGF $< \dot{V}_E$ and complete NO uptake, the N_2O flowmeter delivered a lower [NO] (70 and 40% of the [NO] set at 4 and 2 L/min, respectively) and the INOvent delivered a higher [NO] (10 and 23% higher than the [NO] set at 4 and 2 L/min, respectively). Decreasing the NO uptake increased the inspired [NO] similarly with both systems. At 4 L/min FGF, [NO] increased by 10%–20% with 60% uptake and by 18%–23% with 30% uptake. At 2 L/min, [NO] increased by 30%–33% with 60% uptake and by 60%–69% with 30% uptake. We conclude that intraoperative NO inhalation is accurate when administered either by the N_2O flowmeter of an anesthesia machine or by the INOvent when FGF $\geq \dot{V}_E$. IMPLICATIONS: Inhaled nitric oxide (NO) is a selective pulmonary vasodilator. In a lung model, we demonstrated that NO can be delivered accurately by a N_2O flowmeter or by a commercial device. We provide guidelines for intraoperative NO delivery.

BREATHING SIMULATOR
A Spontaneously Breathing Lung Model

Breathing Simulator in use with a Ventilator

- Simulates spontaneous & passive patients
- Simulates a wide range of lung parameters
- Adjustable airway resistance, lung compliance, breath rate & patient effort
- Mathematical lung model
- Data collection & fast repeatable setups
- Automate tests with a script file

■ *Helps meet new GMP design control requirements*

• Development of respiratory therapy devices • Production testing
• Product training and demonstration • Research and comparative testing

HANS RUDOLPH, inc.
MAKERS OF RESPIRATORY VALVES SINCE 1938
TEL: (816) 363-5522 U.S.A. & CANADA (800) 456-6695
FAX: 816-822-1414 E-Mail: hri@rudolphkc.com www.rudolphkc.com
7205 CENTRAL, KANSAS CITY, MISSOURI 64114 U.S.A.

Circle 131 on reader service card

A Pilot Study of Pharyngeal Pulse Oximetry with the Laryngeal Mask Airway: A Comparison with Finger Oximetry and Arterial Saturation Measurements in Healthy Anesthetized Patients—Keller C, Brimacombe J, Agro F, Margreiter J. Anesth Analg 2000 Feb;90(2): 440–444.

We compared pharyngeal S_{pO_2} by using the laryngeal mask airway (LMA) to finger S_{pO_2} and oxygen saturation from arterial blood samples (S_{aO_2}). We studied 20 hemodynamically stable, well oxygenated, anesthetized patients (ASA physical status I-III, aged 18–80 yr). A single-use pediatric pulse oximeter was attached to the back plate of a size 5 LMA. Pharyngeal and finger S_{pO_2} (dominant index finger) and S_{aO_2} (nondominant radial artery) were measured with the cuff volume at 0–40 mL in the neutral position. The intracuff pressure was then set at 60 cm H_2O in the neutral position, and readings were taken with the head-neck flexed, extended, and rotated. S_{aO_2} was the same as pharyngeal S_{pO_2} at 20 and 30 mL cuff volume, but higher than pharyngeal S_{pO_2} at all other cuff volumes and head-neck positions ($p < 0.04$). S_{aO_2} was always higher than finger S_{pO_2} ($p < 0.01$). Pharyngeal S_{pO_2} was higher than finger S_{pO_2} at cuff volumes 10–40 mL and in the flexed and rotated head-neck positions (all: $p < 0.007$), but was lower at 0 cuff volume ($p < 0.0001$) and similar in the extended head-neck position. There was an increase in pharyngeal S_{pO_2} between 0 and 10 mL cuff volume ($p < 0.0001$), but no changes thereafter. Pharyngeal S_{pO_2} was similar in the flexed, rotated and extended head-neck positions. Pharyngeal S_{pO_2} agrees more closely with S_{aO_2} (mean difference < 0.7%) than finger S_{pO_2} (mean difference > 1.1%) at 10–40 mL cuff volume and in head-neck flexion. The standard error of limits was identical (0.09) for both finger S_{pO_2} and pharyngeal S_{pO_2} if data at 0 cuff volume are excluded. We conclude that pharyngeal

S_{pO_2} with the LMA is feasible and generally provides more accurate readings than finger S_{pO_2} in hemodynamically stable, well oxygenated, anesthetized patients. IMPLICATIONS: Pharyngeal oximetry with the laryngeal mask airway is feasible and generally provides more accurate readings than finger oximetry in hemodynamically stable, well oxygenated, anesthetized patients.

A Controlled Trial of a Critical Pathway for Treatment of Community-Acquired Pneumonia—CAPITAL Study Investigators. Community-Acquired Pneumonia Intervention Trial Assessing Levofloxacin. Marrie TJ, Lau CY, Wheeler SL, Wong CJ, Vandervoort MK, Feagan BG. JAMA 2000 Feb 9;283(6):749–755.

CONTEXT: Large variations exist among hospitals in the use of treatment resources for community-acquired pneumonia (CAP). Lack of a common approach to the diagnosis and treatment of CAP has been cited as an explanation for these variations. OBJECTIVE: To determine if use of a critical pathway improves the efficiency of treatment for CAP without compromising the well-being of patients. DESIGN: Multicenter controlled clinical trial with cluster randomization and up to 6 weeks of follow-up. SETTING: Nineteen teaching and community hospitals in Canada. PATIENTS: A total of 1743 patients with CAP presenting to the emergency department at 1 of the participating institutions between January 1 and July 31, 1998. INTERVENTION: Hospitals were assigned to continue conventional management (n = 10) or implement the critical pathway (n = 9), which consisted of a clinical prediction rule to guide the admission decision, levofloxacin therapy, and practice guidelines. MAIN OUTCOME MEASURES: Effectiveness of the critical pathway, as measured by health-related quality of life on the Short-Form 36 Physical Component Summary (SF-36 PCS) scale at 6 weeks; and resource utilization, as measured by the number of bed days per patient managed (BDPM). RESULTS: Quality of life and the occurrence of complications, readmission, and mortality were not different for the 2 strategies; the 1-sided 95% confidence limit of the between-group difference in the SF-36 PCS change score was 2.4 points, which was within a predefined 3-point boundary for equivalence. Pathway use was associated with a 1.7-day reduction in BDPM (4.4 vs 6.1 days; p = 0.04) and an 18% decrease in the admission of low-risk patients (31% vs 49%; p = 0.01). Although inpatients at critical pathway hospitals had more severe disease, they required 1.7 fewer days of intravenous therapy (4.6 vs 6.3 days; p = 0.01) and were more likely to receive treatment with a single class of antibiotic (64% vs 27%; p< 0.001). CONCLUSION: In this study, implementation of a critical pathway reduced the use of institutional resources without causing adverse effects on the well-being of patients.

Effect of Out-of-Hospital Pediatric Endotracheal Intubation on Survival and Neurological Outcome: A Controlled Clinical Trial—Gausche M, Lewis RJ, Stratton SJ, Haynes BE, Gunter CS, Goodrich SM, et al. JAMA 2000 Feb 9;283(6):783–790.

CONTEXT: Endotracheal intubation (ETI) is widely used for airway management of children in the out-of-hospital setting, despite a lack of controlled trials demonstrating a positive effect on survival or neurological outcome. OBJECTIVE: To compare the survival and neurological outcomes of pediatric patients treated with bag-valve-mask ventilation (BVM) with those of patients treated with BVM followed by ETI. DESIGN: Controlled clinical trial, in which patients were assigned to interventions by calendar day from March 15, 1994, through January 1, 1997. SETTING: Two large, urban, rapid-transport emergency medical services (EMS) systems. PARTICIPANTS: A total of 830 consecutive patients aged 12 years or younger or estimated to weigh less than 40 kg who required airway management; 820 were available for follow-up. INTERVENTIONS: Patients were assigned to receive either BVM (odd days; n = 410) or BVM followed by ETI (even days; n = 420). MAIN OUTCOME MEASURES: Survival to hospital discharge and neurological status at discharge from an acute care hospital compared by treatment group. RESULTS: There was no significant difference in survival between the BVM group (123/404 [30%]) and the ETI group (110/416 [26%]) (odds ratio [OR], 0.82; 95% confidence interval [CI], 0.61–1.11) or in the rate of achieving a good neurological outcome (BVM, 92/404 [23%] vs ETI, 85/416 [20%]) (OR, 0.87; 95% CI, 0.62–1.22). CONCLUSION: These results indicate that the addition of out-of-hospital ETI to a paramedic scope of practice that already includes BVM did not improve survival or neurological outcome of pediatric patients treated in an urban EMS system.

Extracorporeal Life Support: The University of Michigan Experience—Bartlett RH, Roloff DW, Custer JR, Younger JG, Hirschl RB. JAMA 2000 Feb 16;283(7):904–908.

The University of Michigan experience with extracorporeal life support (ECLS) in 1000 consecutive patients between 1980 and 1998 is the largest series at one institution in the world. Among this patient population, survival to hospital discharge in moribund patients with respiratory failure was 88% in 586 neonates, 70% in 132 children, and 56% in 146 adults. Survival in moribund patients with cardiac failure was 48% in 105 children and 33% in 31 adults. This article describes the University of Michigan's overall ECLS patient experience, the progression of ECLS from laboratory experiments to clinical application at the bedside, the expansion of the technology to other centers, and current ECLS technology and outcomes. Despite the challenges faced in clinical research in this field, our experience and that of others has shown that ECLS saves lives of patients with acute cardiac or pulmonary failure in a variety of clinical settings.

Tolerability and Side-Effects of Post-Exposure Prophylaxis for HIV Infection—Parkin JM, Murphy M, Anderson J, El-Gadi S, Forster G, Pinching AJ. Lancet 2000 Feb 26;355(9205):722–723.

A study of HIV post-exposure prophylaxis in 28 recipients showed that indinavir-containing regimens were poorly tolerated. This finding has implications for compliance and efficacy of the currently recommended combinations.

Cigarette Smoking and Invasive Pneumococcal Disease. Active Bacterial Core Surveillance Team—Nuorti JP, Butler JC, Farley MM, Harrison LH, McGeer A, Kolczak MS, Breiman RF. N Engl J Med 2000 Mar 9;342(10):681–689.

BACKGROUND: Approximately half of otherwise healthy adults with invasive pneumococcal disease are cigarette smokers. We conducted a population-based case-control study to assess the importance of cigarette smoking and other factors as risk factors for pneumococcal infections. METHODS: We identified immunocompetent patients who were 18 to 64 years old and who had invasive pneumococcal disease (as defined by the isolation of *Streptococcus pneumoniae* from a normally sterile site) by active surveillance of laboratories in metropolitan Atlanta, Baltimore, and Toronto. Telephone interviews were conducted with 228 patients and 301 control subjects who were reached by random-digit dialing. RESULTS: Fifty-eight percent of the patients and 24 percent of the control subjects were current smokers. Invasive pneumococcal disease was associated with cigarette smoking (odds ratio, 4.1; 95 percent confidence interval, 2.4 to 7.3) and with passive smoking among nonsmokers (odds ratio, 2.5; 95 percent confidence interval, 1.2 to 5.1) after adjustment by logistic-regression analysis for age, study site, and independent risk factors such as male sex, black race, chronic illness, low level of education, and living with young children who were in day care. There were dose-response relations for the current number of cigarettes smoked per day, pack-years of smoking, and time since quitting. The adjusted population

If it's healthcare related, we've got the job for you.
hospitalhub.com is worth a daily click.
• Thousands of healthcare jobs at the country's finest facilities
• Authoritative, up-to-date healthcare news
• Dynamic, free-wheeling discussion areas where healthcare people exchange ideas, information and opinions every day
It's the site for healthcare professionals on the fast track.
"I always recommend hospitalhub.com"
© 2000 Hospitalhub.com
hospitalhub.com
Not online yet? Call us! 888.562.4357

Circle 124 on product info card

INGMAR MEDICAL
Active Servo Lung (ASL 5000) Breathing Simulator
• Spontaneous/ passive
• Adult to neonatal
• Precision lung model & flow generator
• LabVIEW™ based
NEW
For advanced research, product development, and testing of respiratory therapy devices
IngMar Medical ... Expanding the Vision of Respiratory Care
Tel: 800-583-9910 Fax: 412-683-8404
Internet: http://www.ingmarmed.com
Email: info@ingmarmed.com
LabVIEW is a trademark of National Instruments

Circle 104 on product info card

attributable risk was 51 percent for cigarette smoking, 17 percent for passive smoking, and 14 percent for chronic illness. CONCLUSIONS: Cigarette smoking is the strongest independent risk factor for invasive pneumococcal disease among immunocompetent, nonelderly adults. Because of the high prevalence of smoking and the large population attributable risk, programs to reduce both smoking and exposure to environmental tobacco smoke have the potential to reduce the incidence of pneumococcal disease.

Asthma Education and Quality of Life in the Community: A Randomised Controlled Study to Evaluate the Impact on White European and Indian Subcontinent Ethnic Groups from Socioeconomically Deprived Areas in Birmingham, UK—Moudgil H, Marshall T, Honeybourne D. Thorax 2000 Mar;55(3):177–183.

BACKGROUND: Whether asthma morbidity in minority groups can be reduced by preventative health care measures delivered in the relevant ethnic dialects requires further evaluation. This study reports clinical outcomes and quality of life from a community based project investigating white European (W/E) and Indian subcontinent (ISC) ethnic groups with asthma living in deprived inner city areas of Birmingham, UK. METHODS: Six hundred and eighty nine asthmatic subjects (345 W/E, 344 ISC) of mean (SD) age 34.5 (15) years (range 11–59) and mean forced expiratory volume in one second (FEV_1) of 80% predicted were interviewed in English, Punjabi, Hindi, or Urdu. Subjects randomised to the active limb of a prospective, open, randomised, controlled, parallel group, 12 month follow up study underwent individually based asthma education and optimisation of drug therapy with four monthly follow up (active intervention). Control groups were seen only at the beginning and end of the study. Urgent or emergency interactions with primary and secondary health care (clinical outcomes) and both cross sectional and longitudinal data from an Asthma Quality of Life Questionnaire (AQLQ) were analysed. RESULTS: Clinical outcomes were available for 593 subjects. Fewer of the active intervention group consulted their GP (41.8% versus 57.8%, odds ratio (OR) 0.52 (95% CI 0.37 to 0.74)) or were prescribed antibiotics (34.9% versus 51.2%, OR 0.51 (95% CI 0.36 to 0.72)), but by ethnicity statistically significant changes occurred only in the W/E group with fewer also attending A&E departments and requiring urgent home visits. Active intervention reduced the number of hospital admissions (10 versus 30), GP consultations (341 versus 476), prescriptions of rescue oral steroids (92 versus 177), and antibiotics (220 versus 340), but again significant improvements by ethnicity only occurred in the active W/E group. AQLQ scores were negatively skewed to the higher values; regression analysis showed that lower values were associated with ISC ethnicity. Longitudinal changes (for 522 subjects) in the mean AQLQ scores were small but statistically significant for both ethnic groups, with scores improving in the active and worsening in the control groups. CONCLUSIONS: Active intervention only improved clinical outcomes in the W/E group. AQLQ scores, although lower in the ISC group, were improved by active intervention in both ethnic groups.

Airflow Obstruction in Bronchiectasis: Correlation between Computed Tomography Features and Pulmonary Function Tests—Roberts HR, Wells AU, Milne DG, Rubens MB, Kolbe J, Cole PJ, Hansell DM. Thorax 2000 Mar;55(3):198–204.

BACKGROUND: An obstructive defect is usual in bronchiectasis, but the pathophysiological basis of airflow obstruction remains uncertain. High resolution computed tomographic (CT) scanning now allows quantitation of static morphological abnormalities, as well as dynamic changes shown on expiratory CT scans. The aim of this study was to determine which static and dynamic structural abnormalities on the CT scan are associated with airflow obstruction in bronchiectasis. METHODS: The inspiratory and expiratory features on the CT scan of 100 patients with

CINCINNATI USA
"Leading You Beyond Today's Horizons"
Cincinnati Welcomes the American Association for Respiratory Care
46th International Respiratory Congress
October 7-10, 2000 • (972) 243- 2272 • www.aarc.org
Join the AARC in Cincinnati this millennial year as we examine our rich

CINCINNATI USA

Welcomes the

American Association for Respiratory Care
46th International Respiratory Congress
October 7-10, 2000

C ulture…world-class symphony, opera, ballet, museums and theatre.

I nternational airport located only 20 minutes from downtown.

N ightlife…great jazz clubs, riverboat cruises, unique bars and pubs.

C uisine…from 5-way chili to a 5-star restaurant, Cincinnati has more restaurants per capita than any city its size outside of San Francisco.

I nteresting attractions and special event facilities: world famous zoo, Museum Center, Paramount's Kings Island, Coney Island, Krohn Conservatory, Mt. Adams, Music Hall, Bicentennial Commons, & more!

N obody rolls out the barrel like Cincinnati•USA. We're home to wineries and breweries that are open to tours and tastings.

N eighborly welcome from the entire hospitality community!

A ccessibility…less than 60 minutes by air and an easy one-day drive for over 60% of the nation's population.

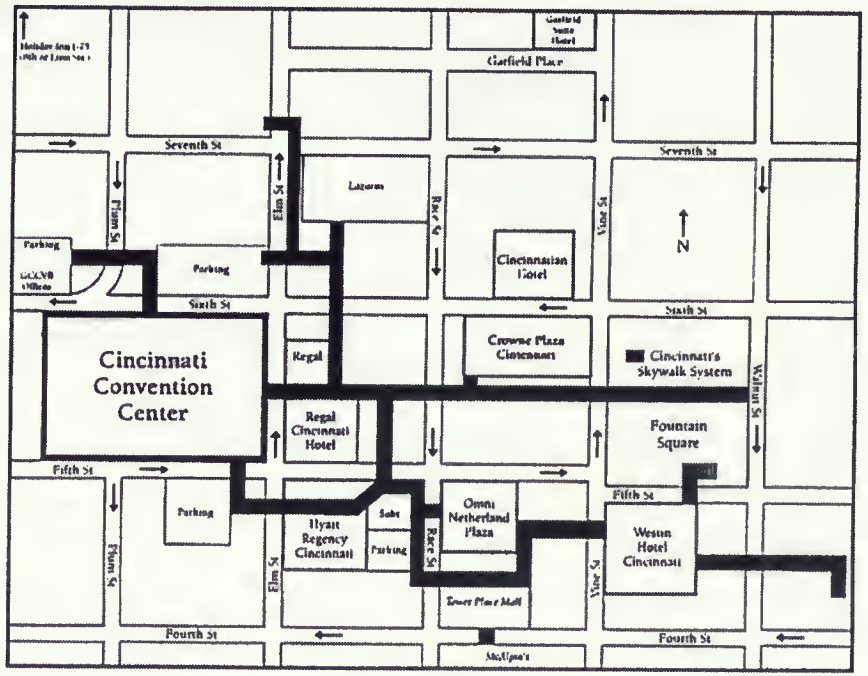
T ransportation…is easy whether taking the airport shuttle or a taxi to enter downtown, or using the second-level pedestrian Skywalk system, getting around is easy.

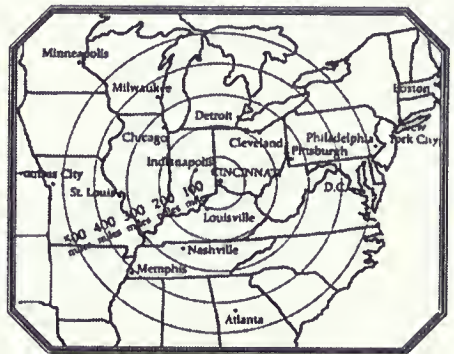
I mpressive…up-to-date Convention Center and inviting hotels that pride themselves on service and hospitality. Downtown hotels are all within 2 1/2 blocks of the Convention Center.

U nique shopping…major department stores such as Saks, McAlpins, Lazarus, Tower Place Mall, nearby antiquing; MainStrasse Village, various outlet malls.

S ports…Cincinnati is home to the Cincinnati Reds, Bengals, Cyclones. Also River Downs, Turfway Race Tracks, and many sporting events.

A ffordability…"BIG" city amenities at affordable prices mean great value!





bronchiectasis undergoing concurrent lung function tests were scored semi-quantitatively by three observers. RESULTS: On univariate analysis the extent and severity of bronchiectasis, the severity of bronchial wall thickening, and the extent of decreased attenuation on the expiratory CT scan correlated strongly with the severity of airflow obstruction; the closest relationship was seen between decreased forced expiratory volume in one second (FEV_1) and the extent of decreased attenuation on the expiratory CT scan (R^2 = -0.55, $p<0.00005$). On multivariate analysis bronchial wall thickness and decreased attenuation were consistently the strongest independent determinants of airflow obstruction. The extent of decreased attenuation was positively associated with the severity of bronchial wall thickness, but was not independently linked to gas transfer levels. Endobronchial secretions seen on CT scanning had no functional significance; the severity of bronchial dilatation was negatively associated with airflow obstruction after adjustment for other morphological features. CONCLUSIONS: These findings indicate that airflow obstruction in bronchiectasis is primarily linked to evidence of intrinsic disease of small and medium airways on CT scanning and not to bronchiectatic abnormalities in large airways, emphysema, or retained endobronchial secretions.

Randomised Prospective Parallel Trial of Therapeutic Versus Subtherapeutic Nasal Continuous Positive Airway Pressure on Simulated Steering Performance in Patients with Obstructive Sleep Apnoea—Hack M, Davies RJ, Mullins R, Choi SJ, Ramdassingh-Dow S, Jenkinson C, Stradling JR. Thorax 2000 Mar;55(3):224–231.

BACKGROUND: Obstructive sleep apnoea (OSA) impairs vigilance and may lead to an increased rate of driving accidents. In uncontrolled studies accident rates and simulated steering performance improve following treatment with nasal continuous positive airway pressure (NCPAP). This study seeks to confirm the improvement in steering performance in a randomised controlled trial using subtherapeutic NCPAP as a control treatment. METHODS: Fifty nine men with OSA (Epworth Sleepiness Score (ESS) of ≥10, and ≥10/h dips in S_{aO_2} of >4% due to OSA) received therapeutic or subtherapeutic NCPAP (approximately 1 cm H_2O) for one month. Simulated steering performance over three 30-minute "drives" was quantified as: standard deviation (SD) of road position, deterioration in SD across the drive, length of drive before "crashing", and number of off-road events. The reaction times to peripheral target stimuli during the drive were also measured. RESULTS: Subtherapeutic NCPAP did not improve overnight >4% S_{aO_2} dips/h compared with baseline values, thus acting as a control. The SD of the steering position improved from 0.36 to 0.21 on therapeutic NCPAP, and from 0.35 to 0.30 on subtherapeutic NCPAP ($p = 0.03$). Deterioration in SD of the steering position improved from 0.18 to 0.06 SD/h with therapeutic NCPAP and worsened from 0.18 to 0.24 with subtherapeutic NCPAP ($p = 0.04$). The reaction time to target stimuli was quicker after therapeutic than after subtherapeutic NCPAP (2.3 versus 2.7 seconds, $p = 0.04$). CONCLUSIONS: Therapeutic NCPAP improves steering performance and reaction time to target stimuli in patients with OSA, lending further support to the hypothesis that OSA impairs driving, increases driving accident rates, and that these improve following treatment with NCPAP.

Ventilation with Lower Tidal Volumes As Compared with Traditional Tidal Volumes for Acute Lung Injury and the Acute Respiratory Distress Syndrome—The Acute Respiratory Distress Syndrome Network. N Engl J Med 2000 May 4;342(18):1301-1308.

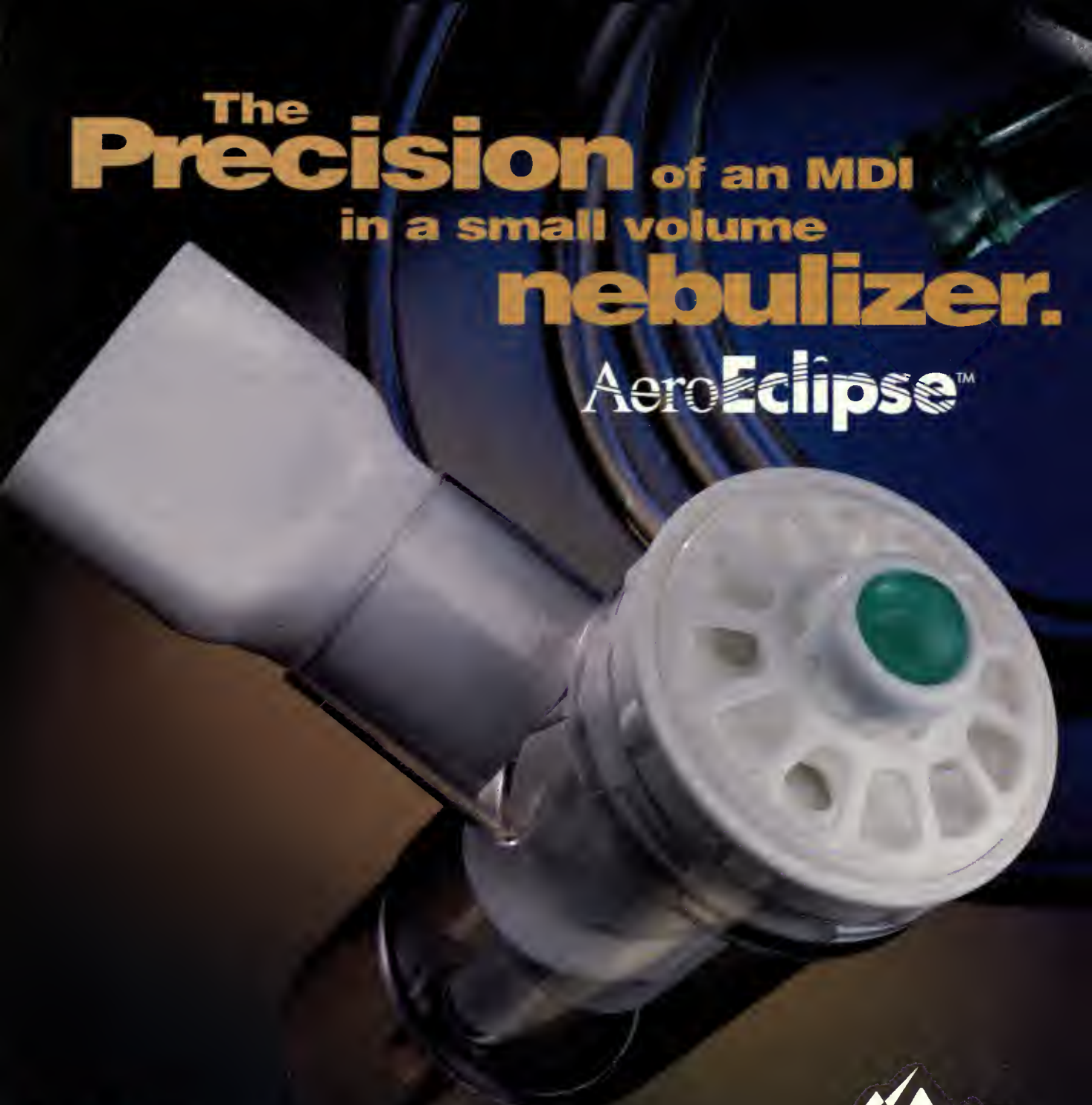
BACKGROUND: Traditional approaches to mechanical ventilation use tidal volumes of 10 to 15 mL per kilogram of body weight and may cause stretch-induced lung injury in patients with acute lung injury and the acute respiratory distress syndrome. We therefore conducted a trial to determine whether ventilation with lower tidal volumes would improve the clinical outcomes in these patients. METHODS: Patients with acute lung injury and the acute respiratory distress syndrome were enrolled in a multicenter, randomized trial. The trial compared traditional ventilation treatment, which involved an initial tidal volume of 12 mL per kilogram of predicted body weight and an airway pressure measured after a 0.5-second pause at the end of inspiration (plateau pressure) of 50 cm of water or less, with ventilation with a lower tidal volume, which involved an initial tidal volume of 6 mL per kilogram of predicted body weight and a plateau pressure of 30 cm of water or less. The primary outcomes were death before a patient was discharged home and was breathing without assistance and the number of days without ventilator use from day 1 to day 28. RESULTS: The trial was stopped after the enrollment of 861 patients because mortality was lower in the group treated with lower tidal volumes than in the group treated with traditional tidal volumes (31.0 percent vs. 39.8 percent, $p = 0.007$), and the number of days without ventilator use during the first 28 days after randomization was greater in this group (mean ± SD], 12 ± 11 vs. 10 ± 11; $p = 0.007$). The mean tidal volumes on days 1 to 3 were 6.2 ± 0.8 and 11.8 ± 0.8 mL per kilogram of predicted body weight ($p < 0.001$), respectively, and the mean plateau pressures were 25 ± 6 and 33 ± 8 cm of water ($p < 0.001$), respectively. CONCLUSIONS: In patients with acute lung injury and the acute respiratory distress syndrome, mechanical ventilation with a lower tidal volume than is traditionally used results in decreased mortality and increases the number of days without ventilator use.

Guidelines for Medical and Health Information Sites on the Internet: Principles Governing AMA Web Sites. American Medical Association—Winker MA, Flanagin A, Chi-Lum B, White J, Andrews K, Kennett RL, et al. JAMA 2000 Mar 22-29;283(12):1600-1606.

Access to medical information via the Internet has the potential to speed the transformation of the patient-physician relationship from that of physician authority ministering advice and treatment to that of shared decision making between patient and physician. However, barriers impeding this transformation include wide variations in quality of content on the Web, potential for commercial interests to influence online content, and uncertain preservation of personal privacy. To address these issues, the American Medical Association (AMA) has developed principles to guide development and posting of Web site content, govern acquisition and posting of online advertising and sponsorship, ensure site visitors' and patients' rights to privacy and confidentiality, and provide effective and secure means of e-commerce. While these guidelines were developed for the AMA Web sites and visitors to these sites, they also may be useful to other providers and users of medical information on the Web. These principles have been developed with the understanding that they will require frequent revision to keep pace with evolving technology and practices on the Internet. The AMA encourages review and feedback from readers, Web site visitors, policymakers, and all others interested in providing reliable quality information via the Web.

Assessing the Need for Reintubation: A Prospective Evaluation of Unplanned Endotracheal Extubation—Razek T, Gracias V, Sullivan D, Braxton C, Gandhi R, Gupta R, et al. J Trauma 2000 Mar;48(3):466-469.

OBJECTIVE: Unplanned endotracheal extubation (UEE) is a common complication in medical intensive care units but very little data about UEE in surgical populations are available. Our hypothesis is that the surgical intensive care unit (SICU) population requires reintubation less frequently compared with the medical intensive care unit population. We prospectively gathered data on patients in a SICU in an attempt to identify the incidence of UEE and to study the need for reintubation after UEE. METHODS: During an 18-month period, we prospectively identified SICU patients from a quality improvement database who required ventilatory support. All patients who self-extubated were included in the



AeroEclipse™ Breath-Actuated Nebulizer ("BAN")

A new technology.
Breath actuation is the most significant advancement in the history of small volume nebulizers (SVN). Only the ***AeroEclipse***™ BAN can deliver the precision of an MDI in an SVN.

Match delivery to demand.
The ***AeroEclipse***™ BAN creates aerosol only in precise response to the patient's inspiratory maneuver. This is *patient on-demand therapy* and means less medication waste, safer environments and clinical dose assurance. Truly exceptional aerosol performance delivers more drug – faster and to the right place – creating a treatment modality without equal.

First time precision.
So why not do it right the first time with the ***AeroEclipse***™ BAN. ... After all, when will you have the time to do it again?

AARC ZENITH AWARD 1999

Now available from:

monaghan

Monaghan Medical Corporation
PO Box 2805 • Plattsburgh, NY 12901-0299
Customer Service 800-833-9653

AeroEclipse is a trademark of Monaghan Medical Corporation.
©1999 Monaghan Medical Corporation

Circle 127 on product info card

study. RESULTS: Fifty-eight of 1,178 intubated patients experienced unplanned extubation 61 times during the 18-month period. A total of 22 patients (36%) required reintubation, whereas 39 patients (64%) did not. Thirty-three patients self-extubated while being actively weaned from ventilatory support. Of these, only 5 patients (15%) required reintubation and 28 patients (85%) did not ($p < 0.01$). CONCLUSION: A total of 85% of patients who self-extubate during the weaning process did not require reintubation in our study. Those who have an F_{IO_2} >50%, a lower P_{aO_2}/F_{IO_2} ratio, had UEE occur by accident, or were not being weaned when UEE occurred required reintubation more frequently. These data suggest that some of our SICU patients are intubated longer than necessary, which may translate into more ventilator related complications, longer ICU stays and increased cost.

The Influence of the Composition of the Nursing Staff on Primary Bloodstream Infection Rates in a Surgical Intensive Care Unit—Robert J, Fridkin SK, Blumberg HM, Anderson B, White N, Ray SM, et al. Infect Control Hosp Epidemiol 2000 Jan;21(1):12-17.

OBJECTIVES: To determine the risk factors for acquisition of nosocomial primary bloodstream infections (BSIs), including the effect of nursing-staff levels, in surgical intensive care unit (SICU) patients. DESIGN: A nested case-control study. SETTING: A 20-bed SICU in a 1,000-bed inner-city public hospital. PATIENTS: 28 patients with BSI (case-patients) were compared to 99 randomly selected patients (controls) hospitalized ≥ 3 days in the same unit. RESULTS: Case- and control-patients were similar in age, severity of illness, and type of central venous catheter (CVC) used. Case-patients were significantly more likely than controls to be hospitalized during a 5-month period that had lower regular-nurse-to-patient and higher pool-nurse-to-patient ratios than during an 8-month reference period; to be in the SICU for a longer period of time; to be mechanically ventilated longer; to receive more antimicrobials and total parenteral nutrition; to have more CVC days; or to die. Case-patients had significantly lower regular-nurse-to-patient and higher pool-nurse-to-patient ratios for the 3 days before BSI than controls. In multivariate analyses, admission during a period of higher pool-nurse-to-patient ratio (odds ratio [OR] = 3.8), total parenteral nutrition (OR = 1.3), and CVC days (OR = 1.1) remained independent BSI risk factors. CONCLUSIONS: Our data suggest that, in addition to other factors, nurse staffing composition (ie, pool-nurse-to-patient ratio) may be related to primary BSI risk. Patterns in intensive care unit nurse staffing should be monitored to assess their impact on nosocomial infection rates. This may be particularly important in an era of cost containment and healthcare reform.

A Prolonged Outbreak of *Pseudomonas Aeruginosa* in a Neonatal Intensive Care Unit: Did Staff Fingernails Play a Role in Disease Transmission?—Moolenaar RL, Crutcher JM, San Joaquin VH, Sewell LV, Hutwagner LC, Carson LA, et al. Infect Control Hosp Epidemiol 2000 Feb;21(2):80-85

OBJECTIVES: To describe an outbreak of *Pseudomonas aeruginosa* bloodstream infection (BSI) and endotracheal tube (ETT) colonization in a neonatal intensive care unit (NICU), determine risk factors for infection, and make preventive recommendations. DESIGN: A 15-month cohort study followed by a case-control study with an environmental survey and molecular typing of available isolates using pulsed-field gel electrophoresis. SETTING AND PATIENTS: Neonates in the NICU of a university-affiliated children's hospital. INTERVENTIONS: Improved hand washing and restriction of use of long or artificial fingernails. RESULTS: Of 439 neonates admitted during the study period, 46 (10.5%) acquired *P aeruginosa*; 16 (35%) of those died. Fifteen (75%) of 20 patients for whom isolates were genotyped had genotype A, and 3 (15%) had genotype B. Of 104 healthcare workers (HCWs) from whom hand cultures were obtained, *P aeruginosa* was isolated from three nurses. Cultures from nurses A-1 and A-2 grew genotype A, and cultures from nurse B grew genotype B. Nurse A-1 had long natural fingernails, nurse B had long artificial fingernails, and nurse A-2 had short natural fingernails. On multivariate logistic regression analysis, exposure to nurse A-1 and exposure to nurse B were each independently associated with acquiring a BSI or ETT colonization with *P aeruginosa*, but other variables, including exposure to nurse A-2, were not. CONCLUSION: Epidemiological evidence demonstrated an association between acquiring *P aeruginosa* and exposure to two nurses. Genetic and environmental evidence supported that association and suggested, but did not prove, a possible role for long or artificial fingernails in the colonization of HCWs' hands with *P aeruginosa*. Requiring short natural fingernails in NICUs is a reasonable policy that might reduce the incidence of hospital-acquired infections.

Comparison of Conventional Surgical Versus Seldinger Technique Emergency Cricothyrotomy Performed by Inexperienced Clinicians—Eisenburger P, Laczika K, List M, Wilfing A, Losert H, Hofbauer R, et al. Anesthesiology 2000 Mar;92(3):687-690.

BACKGROUND: Cricothyrotomy is the ultimate option for a patient with a life-threatening airway problem. METHODS: The authors compared the first-time performance of surgical (group 1) versus Seldinger technique (group 2) cricothyrotomy in cadavers. Intensive care unit physicians (n = 20) performed each procedure on two adult human cadavers. Methods were compared with regard to ease of use and anatomy of the neck of the cadaver. Times to location of the cricothyroid membrane, to tracheal puncture, and to the first ventilation were recorded. Each participant was allowed only one attempt per procedure. A pathologist dissected the neck of each patient and assessed correctness of position of the tube and any injury inflicted. Subjective assessment of technique and cadaver on a visual analog scale from 1 (easiest) to 5 (worst) was conducted by the performer. RESULTS: Age, height, and weight of the cadavers were not different. Subjective assessment of both methods (2.2 in group 1 vs. 2.4 in group 2) and anatomy of the cadavers (2.2 in group 1 vs. 2.4 in group 2) showed no statistically significant difference between both groups. Tracheal placement of the tube was achieved in 70% (n = 14) in group 1 versus 60% (n = 12) in group 2 (P value not significant). Five attempts in group 2 had to be aborted because of kinking of the guide wire. Time intervals (mean ± SD) were from start to location of the cricothyroid membrane 7 ± 9 s (group 1) versus 8 ± 7s (group 2), to tracheal puncture 46 ± 37s (group 1) versus 30 ± 28s (group 2), and to first ventilation 102 ± 42s (group 1) versus 100 ± 46s (group 2) (P value not significant). CONCLUSIONS: The two methods showed equally poor performance.

Effect of Infection Control Measures on the Frequency of Upper Respiratory Infection in Child Care: A Randomized, Controlled Trial—Roberts L, Smith W, Jorm L, Patel M, Douglas RM, McGilchrist C. Pediatrics 2000 Apr;105(4 Pt 1):738-742.

BACKGROUND: Acute upper respiratory infections are common in children who attend child care, and preventing transmission of disease in this setting depends on actions by child care staff. We set out to discover whether transmission of respiratory infections in child care could be reduced by improved infection control procedures. METHODS: We performed a cluster, randomized, controlled trial of an infection control intervention conducted in child care centers in 1 city in Australia. The intervention was training of child care staff about transmission of infection, handwashing, and aseptic nosewiping technique. Implementation of the intervention was recorded by an observer. Illness was measured by parent report in telephone interviews every 2 weeks. RESULTS: There were 311 child-years of surveillance for respiratory symptoms. By multivariable analysis, there was no significant reduction in colds in intervention center children across the full age range. However, a significant

reduction in respiratory illness was present in children 24 months of age and younger. When compliance with infection control practices was high, colds in these children were reduced by 17%. CONCLUSIONS: This trial supports the role of direct transmission of colds in young children in child care. The ability of infection control techniques to reduce episodes of colds in children in child care was limited to children 24 months of age and under.

A Guideline Implementation System Using Handheld Computers for Office Management of Asthma: Effects on Adherence and Patient Outcomes—Shiffman RN, Freudigman Md, Brandt CA, Liaw Y, Navedo DD. Pediatrics 2000 Apr;105(4 Pt 1):767-773.

OBJECTIVE: To evaluate effects on the process and outcomes of care brought about by use of a handheld, computer-based system that implements the American Academy of Pediatrics guideline on office management of asthma exacerbations. DESIGN: A before-after trial with randomly selected, office-based Connecticut pediatricians. In both the control and intervention phases, physicians collected data from 10 patient encounters for acute asthma exacerbations. During the intervention phase, the computer provided for structured encounter documentation and offered recommendations based on the guideline of the American Academy of Pediatrics. Patients were contacted by telephone 7 to 14 days after the visit to assess outcomes. RESULTS: Nine-study physicians enrolled 91 patients in the control phase and 74 in the intervention phase. Follow-up information was available for 93% of encounters. Use of the intervention was associated with increased mean frequency/visit of: 1) measurements of peak expiratory flow rate (2.18 vs 1.57) and oxygen saturation (1.12 vs. 42), and 2) administration of nebulized β_2-agonists (1.25 vs. 71). Visits in the intervention phase lasted longer and fees were higher ($145.61 vs $103.11). There were no significant differences in immediate disposition or subsequent emergency department visits, hospitalizations, missed school, or caretaker's missed work during the 7 days post visit. CONCLUSION: Use of handheld computers that provide guideline-based decision support was associated with increased physician adherence to guideline recommendations; however, visits were prolonged, fees were higher, and no improvement could be demonstrated with regard to the observed intermediate-term patient outcomes. Guideline implementers (and users) should be cautious about putting unvalidated recommendations into practice.

Potential to Prevent Carbon Dioxide Rebreathing of Commercial Products Marketed to Reduce Sudden Infant Death Syndrome Risk—Carolan PL, Wheeler WB, Ross JD, Kemp RJ. Pediatrics 2000 Apr;105(4 Pt 1):774-779.

OBJECTIVE: Rebreathing of exhaled air is one proposed mechanism for the increased risk for sudden infant death syndrome among prone sleeping infants. We evaluated how carbon dioxide (CO_2) dispersal was affected by a conventional crib mattress and 5 products recently marketed to prevent prone rebreathing. SETTING: Infant pulmonary laboratory. EQUIPMENT: An infant mannequin with its nares connected via tubing to a 100-mL reservoir filled with 5% CO_2. The sleep surfaces studied included: firm mattress covered by a sheet, Bumpa Bed, Breathe Easy, Kid Safe/Baby Air, Halo Sleep System, and Sleep Guardian. The mannequin was positioned prone face-down or near-face-down. The sleep surfaces were studied with the covering sheet taut, covering sheet wrinkled, and with the mannequin arm positioned up, near the face. MEASUREMENTS:. We measured the fall in percentage end-tidal CO_2 as the reservoir was ventilated with the piston pump. The half-time for CO_2 dispersal ($t_{1/2}$) is an index of the ability to cause or prevent rebreathing. RESULTS: Compared with the face-to-side control, 5 of 6 surfaces allowed a significant increase in $t_{1/2}$ in all 3 prone scenarios. The firm mattress and 4 of the 5 surfaces designed to prevent rebreathing consistently allowed $t_{1/2}$ above thresholds for the onset of CO_2 retention and lethal rebreathing in an animal model (J Appl Physiol 1995;78:740). CONCLUSIONS: With very few exceptions, infants should be placed supine for sleep. For infants placed prone or rolling to the prone position, significant rebreathing of exhaled air would be likely on all surfaces studied, except one.

Neonatal Assisted Ventilation: Predictors, Frequency, and Duration in a Mature Managed Care Organization—Wilson A, Gardner MN, Armstrong MA, Folck BF, Escobar GJ. Pediatrics 2000 Apr;105(4 Pt 1):822-830.

OBJECTIVES: Reference data are lacking on the frequency and duration of assisted ventilation in neonates. This information is essential for determining resource needs and planning clinical trials. As mortality becomes uncommon, ventilator utilization is increasingly used as a measure for assessing therapeutic effect and quality of care in intensive care medicine. Valid comparisons require adjustments for differences in a patient's baseline risk for assisted ventilation and prolonged ventilator support. The aims of this study were to determine the frequency and length of ventilation (LOV) in preterm and term infants and to develop models for predicting the need for assisted ventilation and length of ventilator support. METHODS: We performed a retrospective, population-based cohort study of 77 576 inborn live births at 6 Northern California hospitals with level 3 intensive care nurseries in a group-model managed care organization. The gestational age-specific frequency and duration of assisted ventilation among surviving infants was determined. Multivariable regression was performed to determine predictors for assisted ventilation and LOV. RESULTS: Of 77 576 inborn live births in the study, 11 199 required admission to the neonatal intensive care unit and of these, 1928 survivors required ventilator support. The proportion of infants requiring assisted ventilation and the median LOV decreased markedly with increasing gestational age. In addition to gestational age, admission illness severity, 5-minute Apgar scores, presence of anomalies, male sex, and white race were important predictors for the need for assisted ventilation. The ability of the models to predict need for ventilation was high, and significantly better than birth weight alone with an area under the receiver operating characteristic curve of 0.90 versus 0.70 for preterm infants, and 0.88 versus 0.50 for term infants. For preterm infants, gestational age, admission illness severity, oxygenation index, anomalies, and small-for-gestational age status were significant predictors for LOV, accounting for 60% of the variance in the length of assisted ventilation. For term infants, oxygenation index and anomalies were significant predictors but only accounted for 29% of the variance. CONCLUSIONS: Considerable variation exists in the utilization of ventilator support among infants of closely related gestational age. In addition, a number of medical risk factors influence the need for, and length of, assisted ventilation. These models explain much of the variance in LOV among preterm infants but explain substantially less among term infants.

Bronchopulmonary Hygiene Physical Therapy in Bronchiectasis and Chronic Obstructive Pulmonary Disease: A Systematic Review—Jones A, Rowe BH. Heart Lung 2000 Mar;29(2):125-135.

OBJECTIVES: This study had two objectives: (1) to examine the effects of bronchopulmonary hygiene physical therapy on patients with chronic obstructive pulmonary disease and bronchiectasis; (2) to determine any differences between manual and mechanical techniques for bronchopulmonary hygiene physical therapy. DESIGN: The study design was a systematic review of the literature that used an exhaustive search for trials and review methods prescribed by the Cochrane Collaboration. Inclusion Criteria: Randomized controlled trials examined patient groups, interventions, and dependent variables. PATIENTS: Patients included those with chronic obstructive pulmonary diseases (emphysema or chronic bronchitis) or bronchiectasis. INTERVENTIONS: Any of the following interventions or combinations thereof were included: manual interven-

NEW VIDEOTAPES

FROM

PROFESSOR'S ROUNDS IN RESPIRATORY CARE

Assessing the Respiratory Patient
Helps you learn proper assessment skills, including observation, interviewing, physical assessment. Also discusses use of the peak flow meter, pulse oximeter, and chest roentgenography in patient assessment. Featuring Woody V. Kageler, MD, and David J. Pierson, MD, FAARC. 90-min. videotape.
Item VC91 $49.95 ($99.00 Nonmembers)

Asthma: Managing the Disease
Takes a proactive look at asthma with the perspective of disease management. You will learn the necessary services for an asthma disease management program, how to cost-effectively implement them, and how to measure success through outcomes measurement. Featuring Patti Joyner, RRT, CCM, and Gretchen Lawrence, BA, RRT. 90-min. videotape.
Item VC92 $49.95 ($99.00 Nonmembers)

Ventilators and Their Management
This program discusses the efficacy of the latest mechanical ventilation technology and techniques. Discusses overdistension lung injury, PEEP in the avoidance of lung injury, strategy to improve patient-ventilator synchrony, and the role of the ventilator in ventilator-associated lung injury. Featuring Dean R. Hess, PhD, RRT, FAARC, and Richard D. Branson, BS, RRT. 90-min. videotape.
Item VC93 $49.95 ($99.00 Nonmembers)

The Role of the Disease Manager
Discusses the special skills that are required to manage information from the multidisciplinary team. Topics include workplace environment, the needs for comprehensive assessment skills, the role of the disease manager, and the planning and implementation process. Featuring Mari Jones, MSN, RN, FNP, RRT, and Richard D. Branson, BS, RRT. 90-min. videotape.
Item VC94 $49.95 ($99.00 Nonmembers)

Coping with the Pediatric Emergency
Provides an overview of how to assess the pediatric patient. Includes discussion on differences in anatomy and physiology of the pediatric respiratory system; recognition of the early signs of respiratory distress; the equipment and preparation needed to deal with respiratory emergencies; and the priorities for management of pediatric respiratory emergencies. Featuring Mark J. Heulitt, MD, FAAP, FCCP, and Richard D. Branson, BS, RRT. 90-min. videotape.
Item VC95 $49.95 ($99.00 Nonmembers)

The Latest Word in the Treatment of COPD
This videotape helps you understand what the barriers are to improved outcomes in COPD. Discusses the role of viral and bacterial infection in COPD exacerbation; the processes for clinical pathways development; and the appropriate ventilator management strategies in severe COPD. Featuring Steve Jenkinson, MD, and Woody V. Kageler, MD. 90-min. videotape.
Item VC96 $49.95 ($99.00 Nonmembers)

PEEP: The State of the Art
Discusses the current concepts that relate to the application of positive end-expiratory pressure (PEEP). Presents discussions on the relationship of PEEP to end-expiratory lung volume and its consequences for gas exchange in acute lung injury and how PEEP can prevent it; the benefits of adding PEEP in the setting of severe airflow obstruction and dynamic hyperinflation; and the selection of PEEP and tidal volume for ventilation of the injured lung. Featuring John J. Marini, MD, and David J. Pierson, MD, FAARC. 90-min. videotape.
Item VC97 $49.95 ($99.00 Nonmembers)

New Developments in Respiratory Drugs, Medications, and Delivery Devices
Helps you identify new aerosolized medications for the treatment of pulmonary diseases, their indications, contraindications, and administration. Also discusses the advantages and disadvantages of commonly used delivery devices for aerosolization of drugs and the improvements that have been made in these devices. Featuring Joseph L. Rau, PhD, RRT, FAARC and Richard D. Branson, BS, RRT. 90-min. videotape.
Item VC98 $49.95 ($99.00 Nonmembers)

ORDER COUPON

Charge to my ☐ Visa ☐ MasterCard Card No. _____ Exp. _____ Signature _____

Payment enclosed $ _____ Charge to Purchase Order No. _____

Name/Institution _____

AARC Member No. _____

Address _____

City/State/Zip _____

Valid AARC Member Number required for member prices.
Prices are subject to change without notice.
Texas Customers Only - Please add 8.25% sales tax.
Texas exempt customers must attach exemption certificate.

Mail to: AARC, 11030 Ables Lane, Dallas, TX 75229-4593
(972) 243-2272 • FAX (972) 484-2720

Item No.	Description	Qty	Amt
		Item Subtotal	
		Shipping	
		Subtotal	
		Tx Sales Tax	
		Total	

CALL (972) 406-4663 OR FAX TO (972) 484-2720 WITH MASTERCARD, VISA, OR PURCHASE ORDER NUMBER

SHIPPING AND HANDLING

Order Total	Ground	AK,HI,PR	2nd Day	Next Day	International
$15.00 or less	$4.25	$12.25	$9.50	$17.50	$39.50*
$15.01 to $25	$5.25	$14.50	$12.00	$22.00	$44.00*
$25.01 to $40	$6.25	$17.00	$14.25	$26.25	$48.25*
$40.01 to $60	$7.25	$19.25	$16.50	$30.50	$52.50*
$60.01 to $80	$8.25	$21.50	$19.00	$35.00	$57.00*
$80.01 to $100	$9.25	$25.00	$23.50	$43.50	$65.50*
$100.01 to $150	$10.25	$30.75	$28.00	$52.25	$74.25*
$150.01 to $200	$12.25	$33.00	$30.25	$56.50	$78.50*
$200.01 to $250	$14.25	$39.00	$36.00	$64.50	$86.50*
$250.01 to $300	$16.25	$44.00	$41.00	$73.75	$95.75*
$300.01 and up	$18.25	$58.50	$55.00	$92.25	$114.25*
$400 or more	$20.25	$64.50	$60.50	$97.25	$119.25*

*International orders require an additional $15 for customs brokerage fee.

Visit www.aarc.org for all your respiratory information needs. For other products visit www.aarc.org/professional_resources/keys/

3 Step Program Helps COPD Patients During National Respiratory Care Week

Celebrate National Respiratory Care Week by helping those with Chronic Obstructive Pulmonary Disease (COPD). COPD is the fourth major cause of death in the United States, so the AARC has teamed with NLHEP to you help to promote nationwide public health education and awareness.

You can make a difference by providing your patients and the public with information about COPD–and, help prevent the disease by performing public spirometry screenings.

Step 1: Start your COPD Awareness Program and Draw Attention with Posters and Table Tents

"Test Your Lungs, Know Your Numbers" Poster — Use this colorful poster to make your patients aware of COPD and advise them to test their lungs and know their FEV_1 and FVC numbers. Full color, 18" x 20." **Item S29** $5.50 (Nonmembers $11.00)

Table Tents with COPD Information — These 3-sided table tents feature information about respiratory care and health tips for COPD patients. Also provides an area that you can personalize with your RC Week events. **Item S17** $12.25 (Nonmembers $17.75)

Step 2: Now that You Have Their Attention, Perform Spirometry

"Test for COPD" Forms — Ready-made forms for public health screenings for COPD. Includes a basic explanation of COPD and spirometry along with 5 screening questions and space for FEV_1 and FVC results. Personalize with your institution's name. Pad of 50.
Item S38 $3.50 (Nonmembers $7.00)

While they are waiting in line for the spirometry test, give them the Respiratory IQ Quiz Tests on COPD - Updated for 2000— Inpatients and outpatients alike will find this "Check Your COPD IQ Test" informative. These true-and-false tests include answers that help you inform your patients. Conveniently packaged in pads of 50 sheets. **Item R60** $7.50 (Nonmembers $10.00)

Step 3: Send Them Home with Knowledge about COPD

Health Tips Sheets - Updated for 2000 —These one-page fact sheets help you provide important COPD health information for your patients. Conveniently packaged in pads of 50 sheets so you can send one home with every patient. Topics Include:
Eating Right: Tips for the COPD Patient. Item R25 $7.50 (Nonmembers $10.00)
Exercising Safely with COPD. Item R35 $7.50 (Nonmembers $10.00)
Lessening the Effects of COPD. Item R36 $7.50 (Nonmembers $10.00)

Bookmarks — Handy bookmark gives your patients a carry-home message about COPD and asthma. These informative bookmarks are always at the ready to tell your patients about COPD. Pass them out to your patients or distribute at health fairs. Pkg of 10. **Item S33** $3.50 (Nonmembers $6.50)

Wrist Wrap Wallet — A wonderful gift for your COPD patients. Promotes respiratory health and exercise while securing keys and other valuables. **Item S13** $3.00 (Nonmembers $5.50)

Stickers – 2" stickers promote COPD wellness. Use them on clothing, letters, or envelopes. "Test Your Lungs, Know Your Numbers" Sticker, Pkg of 50. **Item S21** $5.00 (Nonmembers $8.00)

To Order: Call 972-406-4663
With MasterCard, Visa, or Purchase Order

Shipping and Handling Rates — Must be Included on All Orders

Order Total	Ground	AK,HI,PR	Order Total	Ground	AK,HI,PR
$15 or less	$4.25	$12.25	$100.01 to $150	$10.25	$30.75
$15.01 to $25	$5.25	$14.50	$150.01 to $200	$12.25	$33.00
$25.01 to $40	$6.25	$17.00	$200.01 to $250	$14.25	$39.00
$40.01 to $60	$7.25	$19.25	$250.01 to $300	$16.25	$44.00
$60.01 to $80	$8.25	$21.50	$300.01 to $399.99	$18.25	$58.50
$80.01 to $100	$9.25	$25.00	$400 or more	$20.25	$64.50

****Call for International Rates and Express Rates**

AARC • Order Desk • 11030 Ables Lane, Dallas, TX 75229 • (972) 243-2272 • Fax (972) 484-2720

MAKE YOUR CAREER
SHINE
BRIGHTER

ARLINGTON MEMORIAL HOSPITAL
800 W. Randol Mill Rd., Arlington, TX 76012
800/852-6761 or 817/548-6161. FAX: 817/548-6166
• Respiratory Therapist - FT, 3p-11p

HARRIS METHODIST FORT WORTH
1301 Pennsylvania Ave., Fort Worth, TX 76104
817/882-3913. FAX: 817/882-2865
• Respiratory Therapist - FT & PRN, 12-hr day & night shifts

PRESBYTERIAN HOSPITAL OF DALLAS
8440 Walnut Hill Lane, Suite 300, Dallas, TX 75231
214/345-4251. FAX: 214/345-4003
• RRT - NICU

PRESBYTERIAN HOSPITAL OF KAUFMAN
850 W. Highway 243, Kaufman, TX 75142
972/932-7264. FAX: 972/932-7277
• RRT - FT, 2:30p - 11:00p - cert. required

PRESBYTERIAN HOSPITAL OF WINNSBORO
719 West Coke Rd., Winnsboro, TX 75494
903/342-3960. FAX: 903/342-3952
• CRT - FT

Texas Health Resources is an equal opportunity employer which values and celebrates diversity at all levels of our organization.

TEXAS HEALTH RESOURCES
Come Shine In Our System.
www.texashealth.org

Circle 140 on reader service card

KEEP THE GREEN LIGHT SHINING

Thanks to MDA research, the future looks brighter than ever for more than a million Americans affected by neuromuscular diseases.

1-800-572-1717
MDA®
Muscular Dystrophy Association
www.mdausa.org

tions, such as postural drainage, chest percussion, vibration, chest shaking, directed coughing, or forced exhalation technique. CONTROLS: Controls of the study were as follows: no intervention; placebo; coughing; and mechanical interventions, such as mechanical vibration. RESULTS: The search identified 99 potential trials; inclusion or exclusion analysis left 7, which examined a total of 126 patients. Mean score on trial quality was 1.4 (5 = greatest). Three separate trials (N = 51) found statistically significant effects for bronchopulmonary hygiene physical therapy on sputum production and radioaerosol clearance. No trials (N = 126) found statistically significant effects on pulmonary function variables or differences between manual and mechanical techniques. CONCLUSIONS: Considering the small sizes, low quality, and mixed results from the trials, the research on bronchopulmonary hygiene physical therapy is inconclusive. There is a need for adequately sized, high-quality, randomized controlled trials with uniform patient populations to examine the effects of bronchopulmonary hygiene physical therapy.

Intensive Care Unit Syndrome: A Dangerous Misnomer (review)—McGuire BE, Basten CJ, Ryan CJ, Gallagher J. Arch Intern Med 2000 Apr 10;160(7):906-909.

The terms intensive care unit (ICU) syndrome and ICU psychosis have been used interchangeably to describe a cluster of psychiatric symptoms that are unique to the ICU environment. It is often postulated that aspects of the ICU, such as sleep deprivation and sensory overload or monotony, are causes of the syndrome. This article reviews the empirical support for these propositions. We conclude that ICU syndrome does not differ from delirium and that ICU syndrome is caused exclusively by organic stressors on the central nervous system. We argue further that the term ICU syndrome is dangerous because it impedes standardized communication and research and may reduce the vigilance necessary to promptly investigate and reverse the medical cause of the delirium. Directions for future research are suggested.

Effect of Smoking Cessation on Mortality after Myocardial Infarction: Meta-Analysis of Cohort Studies—Wilson K, Gibson N, Willan A, Cook D. Arch Intern Med 2000 Apr 10;160(7):939-944.

OBJECTIVE: To determine the effect of smoking cessation on mortality after myocardial infarction. DATA SOURCES: English- and non-English-language articles published from 1966 through 1996 retrieved using keyword searches of MEDLINE and EMBASE supplemented by letters to authors and searching bibliographies of reviews. STUDY SELECTION: Selection of relevant abstracts and articles was performed by 2 independent reviewers. Articles were chosen that reported the results of cohort studies examining mortality in patients who quit vs continued smoking after myocardial infarction. DATA EXTRACTION: Mortality data were extracted from the selected articles by 2 independent reviewers. DATA SYNTHESIS: Twelve studies were included containing data on 5878 patients. The studies took place in 6 countries between 1949 and 1988. Duration of follow-up ranged from 2 to 10 years. All studies showed a mortality benefit associated with smoking cessation. The combined odds ratio based on a random effects model for death after myocardial infarction in those who quit smoking was 0.54 (95% confidence interval, 0.46-0.62). Relative risk reductions across studies ranged from 15% to 61%. The number needed to quit smoking to save 1 life is 13 assuming a mortality rate of 20% in continuing smokers. The mortality benefit was consistent regardless of sex, duration of follow-up, study site, and time period. CONCLUSION: Results of several cohort studies suggest that smoking cessation after myocardial infarction is associated with a significant decrease in mortality.

Handwashing Compliance by Health Care Workers: The Impact of Introducing an Accessible, Alcohol-Based Hand Antiseptic—Bischoff WE, Reynolds TM, Sessler CN, Edmond MB, Wenzel RP. Arch Intern Med 2000 Apr 10;160(7):1017-1021.

CONTEXT: Under routine hospital conditions handwashing compliance of health care workers including nurses, physicians, and others (eg, physical therapists and radiologic technicians) is unacceptably low. OBJECTIVES: To investigate the efficacy of an education/feedback intervention and patient awareness program (cognitive approach) on handwashing compliance of health care workers; and to compare the acceptance of a new and increasingly accessible alcohol-based waterless hand disinfectant (technical approach) with the standard sink/soap combination. DESIGN: A 6-month, prospective, observational study. SETTING: One medical intensive care unit (ICU), 1 cardiac surgery ICU, and 1 general medical ward located in a 728-bed, tertiary care, teaching facility. PARTICIPANTS: Medical caregivers in each of the above settings. INTERVENTIONS: Implementation of an education/feedback intervention program (6 in-service sessions per each-ICU) and patient awareness program, followed by a new, increasingly accessible, alcohol-based, waterless hand antiseptic agent, initially available at a ratio of 1 dispenser for every 4 patients and subsequently 1 for each patient. MAIN OUTCOME MEASURE: Direct observation of hand-washing for 1575 potential opportunities monitored over 120 hours randomized for both time of day and bed locations. RESULTS: Baseline handwashing compliance before and after defined events was 9% and 22% for health care workers in the medical ICU and 3% and 13% for health care workers in the cardiac surgery ICU, respectively. After the education/feedback intervention program, handwashing compliance changed little (medical ICU, 14% [before] and 25% [after]; cardiac surgery ICU, 6% [before] and 13% [after]). Observations after introduction of the new, increasingly-accessible, alcohol-based, waterless hand antiseptic revealed significantly-higher handwashing rates ($p < 0.05$), and handwashing compliance improved as accessibility was enhanced before 19% and after 41% with 1 dispenser per 4 beds; and before 23% and after 48% with 1 dispenser for each bed. CONCLUSIONS: Education/feedback intervention and patient awareness programs failed to improve handwashing compliance. However, introduction of easily accessible dispensers with an alcohol-based waterless handwashing antiseptic led to significantly higher handwashing rates among health care workers.

Female Gender Associates with Increased Duration of Intubation and Length of Stay after Coronary Artery Surgery—Butterworth J, James R, Prielipp R, Cerese J, Livingston J, Burnett D. CABG Clinical Benchmarking Database. Anesthesiology 2000 Feb;92(2):414-424.

BACKGROUND: Females have worse outcome than do males after coronary artery bypass grafting; however, gender effects on length of stay (LOS) outcomes, such as duration of intubation or intensive care unit (ICU) LOS, have not been evaluated previously. The authors hypothesized that adjustment for pertinent preoperative covariates would eliminate any significant effect of gender on duration of intubation, LOS in the ICU after extubation, total ICU LOS, postoperative (exclusive of ICU) LOS, or total postoperative LOS. METHODS: Patients undergoing elective or urgent primary coronary artery bypass grafting surgery at 51 academic health centers in 1995 and 1997 were studied. Unique multivariable statistical models were developed for duration of intubation, ICU LOS after extubation, total ICU LOS, and postoperative (exclusive of ICU and total) LOS to test for independent associations with gender. Preoperative but not intraoperative or postoperative variables were included in the model. $P \geq 0.01$ was considered significant. RESULTS: All LOSs were of significantly longer duration in females than in males in both the 1995 (n = 1,064) and 1997 (n = 910) data collections. After covariate adjustment, female sex remained associated with significantly longer duration ICU LOS and total postoperative LOS in both the 1995 (female:male ratios 1.30:1 and 1.13:1, respectively) and the 1997 (female:male ratios 1.19:1 and 1.12:1, respectively) data sets. After covari-

The Sterile Solutions

Recently, the FDA proposed guidelines that require inhalation solutions to be sterile.

That may be news to some companies. But not to DEY. Because we've always been sterile.

In fact, since 1978, DEY has produced high quality sterile inhalation solutions. At prices patients really appreciate.

And we've developed exclusive Patient-Focused Packaging™ that's easy to open, use, and store.

For more information, call 800-755-5560.

the Recognize difference.™

DEY

DEY 2751 Napa Valley Corporate Drive Napa, CA 94558

© 1999 DEY 09-736-00 6/99

Circle 150 on product info card

ate adjustment, duration of intubation and ICU LOS after extubation were of significantly longer duration in women than men in 1995 (female:male ratios 1.22:1 and 1.39:1, respectively), but the differences were not significant in 1997. CONCLUSIONS: Even in the context of accelerated recovery programs, these analyses show that female sex has powerful associations with increased LOS intervals for coronary artery bypass grafting surgery, even after adjustment for preoperative covariates. These effects could result from differences in the ways in which men and women respond to coronary artery disease, anesthesia, and coronary artery bypass grafting surgery, or to bias on the part of healthcare workers.

Combitube: A Study for Proper Use—Urtubia RM, Aguila CM, Cumsille MA. Anesth Analg 2000 Apr;90(4):958-962.

The esophageal-tracheal Combitube (ETC; Kendall-Sheridan Catheter Corp., Argyle, NY) is a new device designed for difficult airways and emergency intubation. The manufacturer recommends that the ETC model 37F SA be used in patients with a height of between 122 and 152 cm. The aim of this study was to evaluate whether ventilation is effective and reliable in patients taller than 152 cm by using the ETC 37F SA in the esophageal position. Also, we evaluated whether the airway protection is adequate and whether direct intubation of the trachea with the ETC inserted in the esophagus is possible. We studied 25 anesthetized, paralyzed adult patients, 150 to 180 cm in height. Methylene blue was given orally to all patients before anesthesia induction. Under direct vision, a ETC 37F SA was inserted in the esophagus of all patients. The pharyngeal balloon inflation volume was titrated to air leak and cuff pressures were measured. During surgery, a laryngoscope was inserted into the pharynx with the pharyngeal balloon deflated and the laryngoscopic view was evaluated by using the Cormack-Lehane scale. The presence of methylene blue in the hypopharynx was investigated by direct laryngoscopic vision. Ventilation was effective and reliable in all 25 patients who were 150 to 180 cm in height(average 169 $\pm$ 7 cm). In addition, a direct relationship between the pharyngeal balloon volume and patient height was established ($p < 0.05$), by using linear regression models. The laryngoscopic view of the glottis was adequate to allow direct tracheal intubation. No trace of methylene blue was detected in the hypopharynx. The ETC Model 37F SA may be used in patients from 122 to 185 cm in height. The trachea could be directly intubated with the ETC in the esophageal position in patients with normal airways. The airway protection appears to be adequate. IMPLICATIONS: The esophageal-tracheal Combitube Model 37F SA may be used in patients from 122 to 185 cm in height. The trachea could be directly intubated with the Combitube in esophageal position in patients with normal airways. The airway protection appears to be adequate.

Consequences of Discharges from Intensive Care at Night—Goldfrad C, Rowan K. Lancet 2000 Apr 1;355(9210):1138-1142.

BACKGROUND: It is generally believed that pressure for beds on intensive care-units (ICUs) has increased in the UK. This study used discharge at night as a proxy measure to investigate pressure. METHODS: Night was defined in two ways: "out of office hours" from 2200 to 0659 h and "the early hours of the morning" from 0000 to 0459 h. The rate of discharge at night was compared for 21 295 adult admissions to 62 ICUs covering the period 1995-98 with 10806 admissions to 26 ICUs covering the period 1988-90. With data solely from 1995-98, the consequences of discharge at night and premature discharge were investigated. FINDINGS: Overall, 2269 (21.0%) admissions did not survive the ICU in 1988-90 compared with 4487 (21.1%) in 1995-98. Of ICU survivors, 2.7% were discharged at night (2200-0659 h) in 1988-90 compared with 6.0% in 1995-98. In 1995-98, night discharges (2200-0659 h) had a higher crude (odds ratio 1.46, 95% CI 1.18-1.80)and case-mix adjusted (1.33, 1.06-1.65) ultimate hospital mortality. Higher odds ratios were observed when the definition of night was 0000-0459 h. Premature discharge was commoner at night, 42.6% vs 5.0% and its importance was apparent when incorporated into the logistic-regression model (premature discharge 1.35, 1.10-1.65; night discharge 1.17, 0.92-1.49). INTERPRETATION: Night discharges from ICU are increasing in the UK. This practice is of concern because patients discharged at night fare significantly worse than those discharged during the day. Night discharges are more likely to be "premature" in the view of the clinicians involved. The implication of these results is that many hospitals have insufficient intensive care beds. In deciding whether or not to invest more resources in intensive care we must, however, consider the cost-utility of this particular service compared with other ways that additional resources could be used.

Bronchodilation in Mechanically Ventilated Patients: How Much Is Enough and How Best to Deliver?

In this issue of Respiratory Care, Duarte et al examine the relative effectiveness of aerosolized β agonist administered to mechanically ventilated patients via metered dose inhaler (MDI) in two doses, 4 puffs and 10 puffs delivered with an in-line spacer, or via small-volume nebulizer (SVN).[1] In this excellent prospective randomized trial, the clinical response, as measured by reductions in airway resistance and intrinsic positive end-expiratory pressure, was similar for 2.5 mg of albuterol via SVN and 4 puffs and 10 puffs of albuterol via MDI. Maximum responses were reached in 10 minutes, and pretreatment values returned after 4 hours. To my knowledge, this is the first study that examines the duration of bronchodilation in critically ill mechanically ventilated patients, and thus justifies the common practice of administering aerosolized β agonists at 4-hour intervals in this patient population.

See The Original Study on Page 817

There are two steps that impact effectiveness of aerosol therapies: production and delivery. The efficiency of production is affected by the specific device used to create the aerosol (nebulizer vs MDI). On a gram-for-gram basis, it appears that administration via MDI with spacer provides greater percent delivery than SVN.[2] However, *this difference is clinically inconsequential*, since by simply giving a greater dose via SVN, maximal and equal levels of bronchodilation can be achieved. The current study reiterates this: 2.5 mg of albuterol via SVN achieved similar maximum responses to 0.4 mg (4 puffs) and 1.0 mg (10 puffs) of albuterol via MDI.

Since the method of aerosol production doesn't much matter (assuming proper techniques and that enough is given), the second, and in my opinion far more important step is the precise method used to *deliver* the already-created aerosol to the airways. The casual reader should be aware that Duarte et al[1] and some previous investigators[2,3] have gone to great lengths to achieve conditions that optimize aerosol delivery. In the current study, secretions were removed from the endotracheal tube before treatments, patients were sedated to achieve "passive ventilation," as determined by a "smooth convex pressure waveform," and patients did not trigger additional breaths; in other words they achieved patient-ventilator synchrony with what is essentially control ventilation. In my intensive care unit, aerosols are rarely administered/delivered during such conditions. Moreover, I reject the notion that we should increase sedatives and/or muscle relax our patients to achieve such conditions for the sole purpose of maximizing aerosol delivery. So reader beware: these observations obtained during study conditions cannot necessarily be extrapolated to care of all of your critically ill patients.

At this juncture it is reasonable to summarize what we know about conditions that favor greater aerosol delivery to the airways:

1. *Patient-ventilator synchrony.* This is probably the single most important factor, but no randomized study has addressed whether clinical effectiveness is superior under the ideal conditions described above than in patients who can trigger the ventilator or cough. In one of our early studies, we purposely *did not* sedate patients beyond their normal care and found the majority of clinical effect was achieved after 5 puffs (airway resistance decreased by 17%) and maximum response (airway resistance further decreased by 9%) was achieved after 15 cumulative puffs of albuterol administered via MDI with spacer.[4] Therefore, under nearly ideal clinical circumstances, 4 puffs of albuterol via MDI or 2.5 mg of albuterol via SVN is clearly enough; but in less than ideal circumstances, greater administered doses may be required to achieve the maximum effect, depending upon the degree of patient-ventilator synchrony and the other factors listed below.

2. *Humidification.* Studies have demonstrated that circuit humidification reduces aerosol delivery by roughly half, compared to dry circuit conditions.[5] However, theoretically, dry gas could provoke more bronchospasm. Moreover, it remains unclear to me whether simply turning off the humidifier during treatments, leaving the circuit tubing moist/wet, actually achieves delivery equal to purely dry conditions that can be produced in bench models.

3. *Lower inspiratory flows.* The data are very convincing that lower inspiratory flow regimes improve aerosol delivery to the airways.[5] However, therapists should take great care, if they use lower inspiratory flows, to do so only during treatments and to monitor static airway pressures carefully, since lower inspiratory flows favor dy-

namic hyperinflation that can be acutely life-threatening to severely bronchospastic patients.

To date, there are no data to demonstrate MDI effectiveness if used without an in-line spacer, and the best-studied spacers to date are those produced by Monaghan Medical.[2–5] The reader should be aware that Monaghan provided monetary support for one of my previous studies.[4] I suspect, and there is evidence, that other spacers can also be effective.[6] But to simply assume that other spacers are effective in the absence of data could lead to completely ineffective treatments, as we showed in our earliest study.[7] In aerosol treatments, "the devil is in the details"; practitioners should assume nothing and require data to demonstrate effectiveness for all devices and techniques used in the clinical arena. We have also learned that when MDIs are used, actuation every 15 seconds is equivalent to every minute.[5]

What doesn't work? Some data suggest that inspiratory pauses do not enhance aerosol delivery.[6] Also, I have been very concerned that some in-line suctioning devices used in most intensive care units trap significant amounts of aerosol.[8] Studies are required to determine which, if any, in-line suction devices impede aerosol delivery; until such time, practitioners should consider removing them during treatments when it is vital that aerosols reach the airways (as in severe status asthmaticus).

Finally, continuous nebulization is used at some institutions for patients with severe asthma. Anecdotally, I have arrived to work to find intubated patients with status asthmaticus receiving up to 15 mg/h of aerosolized albuterol, with resulting tachycardia and lactic acidosis. There are no data to suggest that flooding severely asthmatic patients with β agonists improves their outcomes (or even hastens reduction of airway resistance). Continuous nebulization can "sneak up" on the patient and, before it is realized, the patient has received several hundred milligrams and exhibits overt β agonist toxicity. Without question, β agonists are important treatments for patients with status asthmaticus, but clinicians must remain aware of cumulative doses and the signs of systemic toxicity.

With all that background, what do I suggest? In general, I favor common sense (foremost) and a data-driven approach. I view MDI and SVN as equivalent if used properly, and in our hospital the two are of roughly equal cost when labor costs are factored into calculations. Since MDI has some nuances that require additional therapist proficiency, we primarily use SVN, thereby reducing the number of variables that could negatively impact results. Most importantly, we encourage our therapists to measure airway resistance before and after treatments, to assure an effect. There is no use in wasting the therapists' time in the absence of demonstrated benefit to the patient. Finally, an important question remains unanswered, in that bronchodilators are used in many patients without life-threatening bronchospasm. Do these treatments actually impact outcome? There are, to date, no data to answer that question, so the overall cost-benefit ratio of aerosol therapies should be considered for each individual patient.

Constantine A Manthous MD
Bridgeport Hospital
Bridgeport, Connecticut
Yale University School of Medicine
New Haven, Connecticut

REFERENCES

1. Duarte AG, Momii K, Bidani A. Bronchodilator therapy with metered-dose inhaler and spacer versus nebulizer in mechanically ventilated patients: comparison of magnitude and duration of response. Respir Care 2000 45(6):817–823.
2. Dhand R, Jubran A, Tobin MJ. Bronchodilator delivery by metered-dose inhaler in ventilator-supported patients. Am J Respir Crit Care Med 1995;151(6):1827–1833.
3. Dhand R, Duarte A, Jubran A, et al. Dose-response to bronchodilator delivered by metered-dose inhaler in ventilator-supported patients. Am J Respir Crit Care Med 1996;154(2 Pt 1):388–393.
4. Manthous CA, Chatila W, Schmidt GA, Hall JB. Treatment of bronchospasm by metered-dose inhaler albuterol in mechanically ventilated patients. Chest 1995;107(1):210–213.
5. Fink JB, Dhand R, Grychowski J, et al. Reconciling in vitro and in vivo measurements of aerosol delivery from a metered-dose inhaler during mechanical ventilation and defining efficiency-enhancing factors. Am J Respir Crit Care Med 1999;159(1):63–68.
6. Mouloudi E, Katsanoulas K, Anastasaki M, Askitopoulou E, Georgopoulos D. Bronchodilator delivery by metered-dose inhaler in mechanically ventilated COPD patients: influence of end-inspiratory pause. Eur Respir J 1998;12(1):165–169.
7. Manthous CA, Hall JB, Schmidt G, Wood LDH. Metered-dose inhaler versus nebulized albuterol for treatment of bronchospasm in intubated patients. Am Rev Respir Dis 1993;148(6 Pt 1):1567–1570.
8. Khamiees M, Manthous CA. In-line suction catheters may impede aerosol delivery to mechanically ventilated patients. Chest (2000, in press).

Correspondence: Constantine A Manthous MD, Bridgeport Hospital, 267 Grant Street, PO Box 5000, Bridgeport CT 06610. E-mail: pcmant@bpthosp.org.

Bronchodilator Therapy with Metered-Dose Inhaler and Spacer Versus Nebulizer in Mechanically Ventilated Patients: Comparison of Magnitude and Duration of Response

Alexander G Duarte MD, Keith Momii RRT, and Akhil Bidani MD PhD

OBJECTIVE: Four-hour comparison of the bronchodilator response of albuterol administered via metered-dose inhaler (MDI) with spacer versus small-volume nebulizer (SVN) to mechanically ventilated patients with chronic obstructive pulmonary disease (COPD). DESIGN: Prospective randomized clinical trial. SETTING: Medical intensive care unit in a university hospital. PATIENTS: Thirteen mechanically ventilated COPD patients. INTERVENTION: Albuterol administration of 4 puffs (0.4 mg) or 10 puffs (1.0 mg) via MDI with spacer or 2.5 mg via SVN to mechanically ventilated patients in order to assess the bronchodilator response over 4 hours. MEASUREMENTS AND RESULTS: Mechanically ventilated patients were enrolled in a randomized crossover study wherein one group received 4 puffs (0.4 mg) or 2.5 mg of albuterol and another group received 10 puffs (1.0 mg) or 2.5 mg of albuterol on separate days. Respiratory mechanics measurements were obtained over 4 hours. Total airway resistance declined by 14.4 ± 3.8% after 4 MDI puffs, 18.3 ± 1.8% after 10 MDI puffs, or 13.7 ± 2.6% after 2.5 mg via SVN, compared to baseline ($p < 0.01$). After albuterol delivery, airway resistance remained improved for 90–120 minutes ($p < 0.05$) and returned to baseline by 4 hours with all treatments. CONCLUSION: The airway response to albuterol administration via MDI and SVN to mechanically ventilated patients was similar in magnitude and duration, returning to baseline by 240 minutes. In stable, mechanically ventilated COPD patients, albuterol may be administered via MDI with spacer or via SVN every 4 hours. [Respir Care 2000;45(7):817–823] *Key words: bronchodilator, albuterol, obstructive lung disease, inhalation therapy, aerosols, mechanical ventilation.*

Background

Inhaled bronchodilators are frequently used in the management of mechanically ventilated patients because this route of administration provides the greatest benefit with the least adverse effects. Bronchodilators have traditionally been delivered via small-volume nebulizer (SVN), although factors related to cost and convenience support the use of metered-dose inhaler (MDI) administration to ventilator-supported patients.[1] Several investigators have conducted randomized, controlled trials of limited duration comparing bronchodilator delivery via SVN and MDI to intubated, mechanically ventilated patients.[2–4] However, concerns were raised regarding stability of the radioisotope, the heterogeneous nature of the patient populations, and the techniques of delivery, thereby making interpretation of these studies difficult.[5]

See The Related Editorial on Page 815

Recommendations by a panel of experts regarding dosing of inhaled bronchodilators to intubated, mechanically ventilated patients suggested individualizing therapy according to the severity of disease through "dose increases. . . titrated to carefully monitored objective responses."[6] Though titration to a physiologic response is appealing, tachyarrhythmias have been reported with this approach.[3]

Alexander G Duarte MD, Keith Momii RRT, and Akhil Bidani MD PhD are affiliated with the Division of Pulmonary and Critical Care Medicine and Department of Pulmonary Care, University of Texas Medical Branch. Galveston, Texas.

Correspondence: Alexander G Duarte MD, Division of Pulmonary and Critical Care Medicine, University of Texas Medical Branch, John Sealy Annex, 301 University Boulevard, Galveston TX 77555-0561. E-mail: aduarte@utmb.edu.

Furthermore, several investigators have reported significant dose responses to inhaled bronchodilator administration via either MDI or SVN.[7–9] These reports have assisted in the formulation of guidelines for bronchodilator delivery to ventilator-supported patients. However, there are little data addressing the duration of action.[5] Accordingly, we conducted a prospective, randomized, controlled trial to compare the airway response of albuterol administration via MDI with spacer and via SVN over a 4-hour interval in mechanically ventilated patients using a standard ventilator setup.

Materials and Methods

Patients

Thirteen patients with chronic obstructive pulmonary disease (COPD), as defined by the American Thoracic Society guidelines, were enrolled in the study.[10] The etiologies of acute respiratory failure were upper respiratory tract infection (n = 8), pneumonia (n = 2), airway obstruction (n = 2), and pulmonary embolism (n = 1). Pulmonary function studies were available for 5 patients (mean forced expiratory volume in the first second [FEV_1] = 1.01 mL, range 0.48–1.63 mL). The mean age was 63 ± 3 years, with the majority being male (Table 1). Less than one third of the group (4/13) were previously intubated for respiratory failure, and 9/13 had been prescribed domiciliary oxygen within the past 3 months. Patients were studied during stable phases of their intensive care unit courses, and those with a history of asthma, angina, life threatening arrhythmias, myocardial infarction within the past 3 months, or hemodynamic instability were excluded. The diagnosis of asthma was based on the medical history, and because pulmonary function studies were not available for all patients, it is conceivable that some patients with asthma may have been enrolled. All patients received intravenous steroids as part of their medical regimen, and one patient received an aminophylline infusion. The study was approved by the investigational review board, and signed, written, informed consent was obtained from all patients.

Table 1. Patient and Mechanical Ventilator Profile*

Age (y)	63 ± 3
V_T (mL)	630 ± 22
f (breaths/min)	12.0 ± 0.4
$\dot{V}_E$ (L/min)	7.5 ± 0.4
F_{IO_2}	0.35 ± 0.03
T_I (s)	0.65 ± 0.01
T_E (s)	4.50 ± 0.02
T_I/T_{TOT}	0.13 ± 0.01

*Values are mean ± standard error.
V_T = tidal volume. f = respiratory frequency. V_E = minute ventilation. F_{IO_2} = fraction of inspired oxygen. T_I = inspiratory time. T_E = expiratory time. T_I/T_{TOT} = duty cycle (ratio of inspiratory time to total breathing cycle time).

Protocol

Mechanical ventilation was instituted with a BEAR 1000 ventilator (Bear Medical Systems, Riverside, California) using constant inspiratory flow and volume. Inspired gas was heated to 35 ± 1° C and humidified to 98 ± 2% relative humidity using a heated-wire circuit (Isothermal circuit, Allegiance Healthcare, McGaw Park, Illinois) throughout the study. Bronchodilators were withheld 4 hours prior to the study. Prior to commencing, tracheal secretions were removed from the endotracheal tube. Patients were sedated with continuous infusions of lorazepam (n = 10) or propofol (n = 3) and received the same form of sedation during the two arms of the study. Passive ventilation was achieved by increasing delivered tidal volume (V_T) to 500–1000 mL. Passive ventilation was defined as absence of a negative deflection in the pressure tracing prior to inspiration, a smooth convex pressure waveform, and matching ventilator and patient respiratory rate.[11] A randomized crossover design was used, whereby patients were randomly selected to receive albuterol via MDI or SVN (Misty-Neb, Allegiance Healthcare, McGaw Park, Illinois) on Day 1, followed by the alternate method of administration 24 hours later. Patients selected to receive albuterol via MDI were randomly assigned to receive 4 puffs (0.4 mg) or 10 puffs (1.0 mg) via a chamber style spacer (Aerovent, Monaghan Medical, Plattsburgh, New York). All but one patient received albuterol via MDI and SVN, and that patient received medication only via MDI. The albuterol MDI canister (Glaxo Wellcome, Research Triangle Park, North Carolina) (manufacturer-estimated dose of 100 μg/puff) was warmed to hand temperature, well shaken, primed, and discharged into the Aerovent chamber, which was in the inspiratory limb of the ventilator circuit 10 cm from the endotracheal tube. Each actuation was performed at the onset of inspiration, with successive doses actuated from the MDI at 30-second intervals. The SVN (Misty-Neb) was attached to the ventilator circuit 30 cm from the endotracheal tube. The nebulizer cup was filled with 2.5 mg of albuterol sulfate and normal saline (Dey Laboratories, Napa, California) (for a total volume of 3 mL) and driven by an external gas compressor at 50 psi. The SVN was operated continuously at a flow of 6 L/min and intermittently tapped until it sputtered without interruption.

Airway Measurements

Once passive ventilation was achieved, airway measurements were obtained using a respiratory monitor (BiCore, Irvine, California). Pressure, flow, and volume measure-

ments were collected using a precalibrated pneumotachograph attached to the end of the endotracheal tube. The pressure and flow signals were continuously digitized at 50 and 100 Hz, respectively, using a 12-bit analog-to-digital converter linked to a computer, and were stored for later analysis. Airway measurements were obtained prior to administration and at 10, 30, 60, 90, 120, 150, 180, 210, and 240 minutes after albuterol administration. Airway measurements consisted of 5–8 rapid end-inspiratory and end-expiratory airway occlusions performed during the previously mentioned time points. Heart rate, blood pressure, oxygen saturation, and cardiac rhythm were continuously monitored and recorded.

Respiratory Mechanics Calculations

Representative breaths were selected and studied to determine the corresponding airway pressures. During an end-inspiratory occluded breath, peak and plateau airway pressures were determined. Initial pressure was obtained by intersection of the peak airway pressure and a tangent back-extrapolated from the plateau pressure.[11,12] Intrinsic positive end-expiratory pressure ($PEEP_I$) was determined as the static pressure during an end-expiratory occlusion. Total or maximum airway resistance (Rrs_{max}) was calculated as the difference between peak and plateau pressures, divided by the inspiratory flow. The ohmic resistance of the airway or minimum airway resistance (Rrs_{min}) was calculated as the difference between peak and initial pressures, divided by the inspiratory flow. Resistance (ΔRrs) resulting from tissue viscoelastance and time constant differences was calculated as the difference between Rrs_{max} and Rrs_{min}. The percent change in resistance was calculated as the difference between the pre-bronchodilator and post-bronchodilator values divided by the pre-bronchodilator value. Static lung compliance was calculated as the delivered V_T divided by the difference between plateau pressure and $PEEP_I$. Calculations were performed for each timed measurement point.

Statistical Analysis

Results are expressed as mean ± standard errors. Respiratory mechanics measurements and vital signs prior to drug administration were compared with values obtained after albuterol administration, using one-way analysis of variance (ANOVA) with repeated measures and the Tukey test for multiple comparisons between individual means, when appropriate. Comparison of the changes in respiratory mechanics on Day 1 and Day 2 was performed using ANOVA. Statistical analysis was performed using SigmaStat for Windows, Version 2.0 (Jandel, San Rafael, California).

Table 2. Baseline Pulmonary Mechanics*

	MDI 0.4 mg	MDI 1.0 mg	SVN 2.5 mg
Rrs_{max} (cm H_2O/L/s)	18.0 ± 1.3	18.1 ± 1.3	18.4 ± 1.2
Rrs_{min} (cm H_2O/L/s)	16.1 ± 1.3	16.8 ± 1.1	16.7 ± 1.1
ΔRrs (cm H_2O/L/s)	1.9 ± 0.5	1.4 ± 0.8	1.7 ± 0.8
C_{st} (mL/cm H_2O)	28 ± 6	32 ± 8	29 ± 4
$PEEP_I$ (cm H_2O)	9.4 ± 2.4	18.1 ± 1.5†	12.9 ± 2.3

*Values are mean ± standard error. Rrs_{max} = maximum airway resistance. Rrs_{min} = minimum airway resistance. ΔRrs = tissue resistance, time constant differences. C_{st} = compliance. $PEEP_I$ = intrinsic positive end-expiratory pressure.
†0.4 mg vs 1.0 mg, $p < 0.01$.

Results

Baseline airway resistances were similar among the groups ($p > 0.7$) (Table 2). The greatest decrease in Rrs_{max} occurred 10 minutes after albuterol administration of 4 puffs (0.4 mg) or 10 puffs (1.0 mg) via MDI with spacer or 2.5 mg via SVN ($p < 0.01$) (Fig. 1). Following administration of 4 puffs or 10 puffs via MDI or 2.5 mg via SVN, Rrs_{max} decreased by 14.4 ± 3.8%, 18.3 ± 1.8%, and 13.7 ± 2.6%, respectively, compared to baseline ($p < 0.01$). The decrease in Rrs_{max} was 5–33% after 4 puffs, 5–22% after 10 puffs, and 3–33% after 2.5 mg of albuterol. Similarly, minimum (or the true ohmic) airway resistance (Rrs_{min}) decreased significantly after 4 puffs (decrease of 15.9 ± 4.6%), 10 puffs (decrease of 19.8 ± 2.5%), or 2.5 mg (decrease of 14.5 ± 2.5%), compared to baseline ($p < 0.01$) (Fig. 2). Compared to baseline, there was no significant difference in the mean maximum percent decrease in Rrs_{max} and Rrs_{min} following either MDI or SVN administration.

Total Rrs_{max} remained significantly decreased for 90–120 minutes after 4 puffs, 10 puffs, or 2.5 mg via SVN ($p < 0.05$) (see Fig. 1). By 240 minutes after MDI or SVN delivery, Rrs_{max} returned to baseline (see Fig. 1). Similarly, Rrs_{min} remained significantly decreased 90–120 minutes after albuterol delivery, and returned to baseline by 240 minutes. A comparison of the percent decrease in airway resistance among the three groups revealed no significant difference with respect to albuterol dose over time ($p > 0.05$).

Baseline $PEEP_I$ was greater in the group receiving 10 puffs of albuterol than in the group receiving 4 puffs ($p < 0.01$) or 2.5 mg via SVN (not significant). Compared to baseline, $PEEP_I$ declined significantly with administration of 4 puffs, 10 puffs, or 2.5 mg of albuterol, with the greatest decrease occurring 10 minutes after albuterol delivery ($p < 0.05$). $PEEP_I$ remained significantly diminished 90 minutes after drug delivery with either dose or device ($p < 0.05$). Compared to baseline, ΔRrs did not

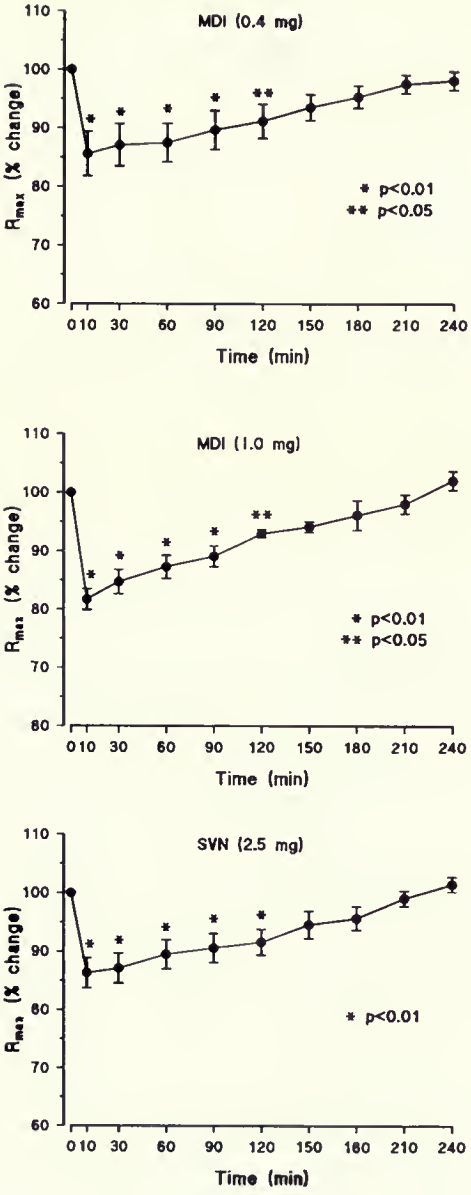


Fig. 1. Change in total (or maximum) airway resistance (Rrs_{max}) after albuterol administration of (top) 4 puffs (0.4 mg) via MDI with spacer, (middle) 10 puffs (1.0 mg) via MDI with spacer, and (bottom) 2.5 mg via SVN, in ventilator-supported COPD patients. Rrs_{max} significantly declined from baseline ($p < 0.01$) and the response was sustained for 120 minutes ($p < 0.05$), returning to baseline within 240 minutes of MDI or SVN albuterol administration. The airway response was similar for albuterol dose or delivery device. Values are means and error bars represent standard error of the mean.

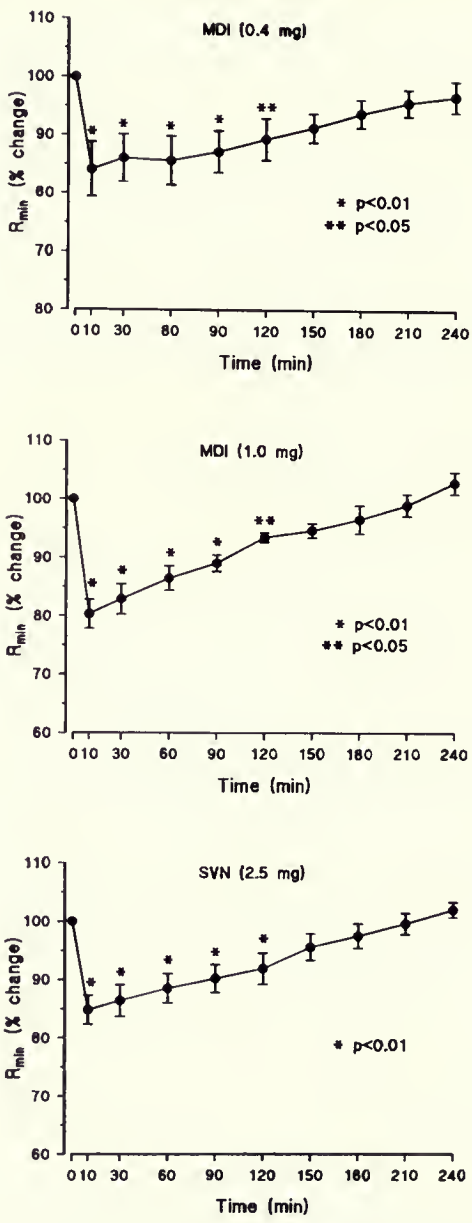


Fig. 2. The effect on minimum airway resistance (Rrs_{min}) after albuterol administration of (top) 4 puffs (0.4 mg) via MDI with spacer, (middle) 10 puffs (1.0 mg) via MDI with spacer, and (bottom) 2.5 mg via SVN to mechanically ventilated COPD patients. A significant decline in Rrs_{min} occurred at 10 minutes and was sustained for 120 minutes, returning to baseline within 240 minutes of MDI or SVN albuterol administration. The airway response was similar among the albuterol doses and delivery devices. Values are means and error bars represent standard error of the mean.

decline significantly after MDI or SVN albuterol delivery. There was no significant change in static lung compliance following MDI or SVN albuterol administration. After albuterol delivery, heart rate, blood pressure, and oxygen saturation were not significantly different than baseline values (Table 3).

Discussion

Although several investigators have examined the action of inhaled bronchodilators in mechanically ventilated patients, we were interested in evaluating the duration of bronchodilator response over 4 hours. We conjectured that

Table 3. Patient Hemodynamics and Oximetry Profile*

	MDI - 0.4 mg		MDI - 1.0 mg		SVN - 2.5 mg	
	Baseline	10 min	Baseline	10 min	Baseline	10 min
HR (beats/min)	77.8 ± 5.1	76.8 ± 5.9	89.7 ± 6.8	91.2 ± 5.4	77.7 ± 5.2	79.4 ± 5.0
MAP (mm Hg)	86.4 ± 2.8	87.1 ± 2.7	93.5 ± 6.6	88.5 ± 5.9	86.5 ± 5.1	89.2 ± 5.0
S_{pO_2} (%)	98.0 ± 0.4	97.7 ± 0.5	97.8 ± 0.7	97.4 ± 0.8	97.4 ± 0.5	97.1 ± 0.7

*Values are mean ± standard error.
HR = heart rate. MAP = mean arterial pressure. S_{pO_2} = arterial oxygen saturation measured via pulse oximetry.

in mechanically ventilated COPD patients the duration of bronchodilator response would be different than in nonintubated patients because of differences in aerosol administration, the presence of an endotracheal tube, or difference in the degree of airway inflammation. To our knowledge, a study of the bronchodilator response beyond 2 hours in ventilator-supported patients has not been previously conducted. Several groups have evaluated the bronchodilator response in ventilator-dependent patients for 30–120 minutes following MDI or SVN delivery.[3,4,7,9,13–16] However, it was unclear from these reports whether the bronchodilator duration of action would persist beyond 120 minutes in ventilator-supported patients. In the present study, we observed a significant decrease in airway resistance for 120 minutes, and resistance returned to baseline within 240 minutes of albuterol delivery. This bronchodilator response profile differs from a previous report in nonintubated COPD or asthma patients.[17] Our findings serve as a useful guide in establishing bronchodilator dosing schedules in stable, mechanically ventilated COPD patients. However, rigid application of this dosing regimen to every ventilator-supported patient would be too simplistic, and under other circumstances more frequent dosing may be required.

Another finding was the similar bronchodilator response profiles following delivery of 0.4 mg via MDI and 2.5 mg of SVN albuterol to mechanically ventilated patients. The maximum airway resistance at baseline was comparable to previously reported values in mechanically ventilated patients.[7,11] Similarly, other authors have reported a rapid onset of action following bronchodilator administration.[13–15,18] However, direct comparison studies examining the peak airway response after MDI and SVN bronchodilator administration to mechanically ventilated patients have yielded various results.[2–4,14] Recently, Guerin et al reported similar decreases in Rrs_{max} 30 minutes after MDI or SVN administration of fenoterol and ipratropium to ventilator-supported COPD patients.[14] They observed a decline in resistance (ΔRrs) because of tissue viscoelasticity and time constant differences following SVN administration, and concluded this was due to greater peripheral pulmonary drug deposition. We observed a decrease in Rrs_{max} but no decline in ΔRrs following MDI or SVN albuterol administration. The observed differences between the studies may be because Guerin et al[14] simultaneously delivered a β agonist and anticholinergic solution, producing a central and peripheral airway response. Additionally, had the peak anticholinergic effect been assessed at 60 minutes rather than at 30 minutes, a similar finding may have been noted following MDI and SVN administration. Nonetheless, a clinically significant airway response may be obtained by selection of an efficient aerosol delivery device in conjunction with a reliable technique of administration.

We speculate that the resemblance between the response profiles following 0.4 mg, 1.0 mg, and 2.5 mg of albuterol may be related to the shallowness of the bronchodilator dose response curve. There are also other factors to explain this observation, such as the genetics of the β receptor, drug distribution, and deposition in the lower airways. Lack of further significant bronchodilator effect with increasing doses of inhaled β agonist is characteristic of the log-linear response, such that a 10-fold increase in the dose is required to achieve a doubled effect.[19] Furthermore, other investigators have demonstrated that the addition of doses exceeding 2.5 mg of albuterol via SVN or 4 puffs via MDI to stable, mechanically ventilated patients provides little further clinically important bronchodilation.[3,8] We recognize that a limitation of this study involves the relatively small number of study patients, and it is conceivable that a larger population might show small differences in response between doses and administration techniques. Yet, it is remarkable that the airway response profile was characteristically similar following 3 separate bronchodilator doses.

Given the similar clinical responses following MDI or SVN bronchodilator administration to ventilator-supported patients, it would appear that the MDI with spacer combination was a more efficient delivery device than the Misty-Neb nebulizer. This is illustrated by the fact that a significant change in airway resistance was observed following MDI administration of a nominal dose 2.5–6 times less than the nebulizer dose. The disparity between the MDI and SVN nominal drug doses is due to losses stemming from drug retention in the nebulizer receptacle

(~50%) and aerosol exhalation during continuous nebulization.[1]

We designed this study to compare the airway response to albuterol administration under common clinical conditions, while attempting to optimize drug delivery. Although a number of actuator devices are commercially available, we selected an MDI and spacer reported to provide adequate deposition and a clinically significant response.[15,20] Selection of the Misty-Neb nebulizer was based on its widespread clinical use and published performance compared with other commonly used commercial units.[21] In addition, we addressed the technique of aerosol administration as this influences lower respiratory tract deposition, and selected an MDI technique of delivery demonstrating substantial respiratory tract deposition and airway response.[15,22–24] Other methods of MDI delivery techniques involve application of an end-inspiratory pause or disconnection of the ventilator circuit followed by manual delivery of a large tidal breath.[4,13,25] However, lack of proven benefit following an end-inspiratory hold maneuver and the potential development of nosocomial airway infection limit these techniques.[25,26] Likewise, the nebulizer technique of administration was similar to previous reports.[3,5,7] Data gathered from bench model studies indicate improvements in respiratory tract delivery, with increased V_T, prolonged duty cycle, dry ventilator circuits, and use of an inspiration-triggered nebulizer.[23,27–30] However, selection of a technique of administration during mechanical ventilation requires a compromise between mechanical ventilator settings and the operating characteristics of the aerosol generating device.[5] Thus, we employed a common ventilator strategy in which V_T ranged from 6–8 mL/kg, producing readily tolerated duty cycles, and sufficient heat and humidity were applied to the respiratory system in order to not worsen pre-existing hyperinflation and airway irritation. In addition, use of continuous nebulization was based on the fact that approximately 30 minutes are required for complete aerosolization with an inspiration-triggered system, and this would have affected our ability to adequately compare the peak responses. After taking into account the different aerosol generating devices, the various techniques of administration, and the mechanical ventilation settings, we demonstrated a similar bronchodilator response following delivery via SVN or MDI with spacer.

Conclusions

In summary, we found a similar pattern of bronchodilator response following albuterol administration of 4 puffs or 10 puffs via MDI with spacer or 2.5 mg via SVN to mechanically ventilated COPD patients. The airway response to albuterol administration via MDI and SVN was similar in magnitude and duration, returning to baseline within 240 minutes. Thus, albuterol may be administered via inhalation on a 4-hour dosing schedule to stable ventilator-supported COPD patients.

Finally, it should be kept in mind that the conditions under which this study was performed were nearly ideal and may not necessarily replicate everyday practice in administering bronchodilators to mechanically ventilated patients.

ACKNOWLEDGMENTS

The authors would like to thank Jamie Grady PhD for assistance and to acknowledge the support of the nursing and respiratory care staff in the medical intensive care unit at the University of Texas Medical Branch in Galveston.

REFERENCES

1. Gross NJ, Jenne JW, Hess D. Bronchodilator therapy. In: Tobin MJ, editor. Principles and practice of mechanical ventilation. New York: McGraw-Hill; 1994; 1023–1077.
2. Fuller HD, Dolovich MB, Posmituck G, Pack WW, Newhouse MT. Pressurized aerosol versus jet aerosol delivery to mechanically ventilated patients: comparison of dose to the lungs. Am Rev Respir Dis 1990;141(2):440–444.
3. Manthous CA, Hall JB, Schmidt GA, Wood LDH. Metered-dose inhaler versus nebulized albuterol in mechanically ventilated patients. Am Rev Respir Dis 1993;148(6 Pt 1):1567–1570.
4. Gay PC, Patel HG, Nelson SB, Gilles B, Hubmayr RD. Metered-dose inhalers for bronchodilator delivery in intubated, mechanically ventilated patients. Chest 1991;99(1):66–71.
5. Dhand R, Tobin MJ. Inhaled bronchodilator therapy in mechanically ventilated patients. Am J Respir Crit Care Med 1997;156(1):3–10.
6. American Association for Respiratory Care. Aerosol consensus statement—1991. Respir Care 1991;36(9):916–921.
7. Bernasconi M, Brandolese R, Poggi R, Manzin E, Rossi A. Dose-response effects and time course of effects of inhaled fenoterol on respiratory mechanics and arterial oxygen tension in mechanically ventilated patients with chronic airflow obstruction. Intensive Care Med 1990;16(2):108–114.
8. Manthous CA, Chatila W, Schmidt GA, Hall JB. Treatment of bronchospasm by metered-dose inhaler albuterol in mechanically ventilated patients. Chest 1995;107(1):210–213.
9. Dhand R, Duarte AG, Jubran A, Jenne JW, Fink JB, Fahey PJ, Tobin MJ. Dose-response to bronchodilator delivered by metered-dose inhaler in ventilator-supported patients. Am J Respir Crit Care Med 1996;154(2 Pt 1):388–393.
10. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1995;152(5 Pt 2):S77–121.
11. Jubran A, Tobin MJ. Passive mechanics of lung and chest wall in patients who failed or succeeded in trials of weaning. Am J Respir Crit Care Med 1997;155(3):916–921.
12. Bates JHT, Milic-Emili J. The flow interruption technique for measuring respiratory resistance. J Crit Care 1991;6:227–238.
13. Fernandez A, Lazaro A, Garcia A, Aragon C, Cerda E. Bronchodilators in patients with chronic obstructive pulmonary disease on mechanical ventilation: utilization of metered-dose inhalers. Am Rev Respir Dis 1990;141(1):164–168.
14. Guerin C, Chevre A, Dessirier P, Poncet T, Becquemin M-H, Dequin P, et al. Inhaled fenoterol-ipratropium bromide in mechanically ventilated patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1999;159(4 Pt 1):1036–1042.
15. Dhand R, Jubran A, Tobin MJ. Bronchodilator delivery by metered-dose inhaler in ventilator-supported patients. Am J Respir Crit Care Med 1995;151(6):1827–1833.

16. Wright PE, Carmichael LC, Bernard GR. Effect of bronchodilators on lung mechanics in the acute respiratory distress syndrome (ARDS). Chest 1994;106(5):1517–1523.
17. Riding WD, Dinda P, Chatterjee SS. The bronchodilator and cardiac effects of five pressure-packed aerosols in asthma. Br J Dis Chest 1970;64(1):37–45.
18. Morina P, Herrera M, Venegas J. Effects of nebulized salbutamol on respiratory mechanics in adult respiratory distress syndrome. Intensive Care Med 1997;23(1):58–64.
19. Nelson HS, Spector SL, Whitsett TL, George RB, Dwek JH. The bronchodilator response to inhalation of increasing doses of aerosolized albuterol. J Allergy Clin Immunol 1983;72(4):371–375.
20. Fuller RW, Dolovich MB, Turpie FH, Newhouse MT. Efficiency of bronchodilator aerosol delivery to the lungs from metered dose inhaler in mechanically ventilated patients: a study comparing four different actuator devices. Chest 1994;105(1):214–218.
21. Hess D, Fisher D, Williams Pooler S, Kacmarek RM. Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer brand. Chest 1996;110(2):498–505.
22. Duarte AG, Dhand R, Reid R, Fink JB, Fahey PJ, Tobin MJ, Jenne JW. Serum albuterol levels in mechanically ventilated patients and healthy subjects after metered-dose inhaler administration. Am J Respir Crit Care Med 1996;154(6 Pt 1):1658–1663.
23. Fink JB, Dhand R, Duarte AG, Jenne JW, Tobin MJ. Aerosol delivery from a metered-dose inhaler during mechanical ventilation: an in vitro model. Am J Respir Crit Care Med 1996;154(2 Pt 1):382–387.
24. Diot P, Morra L, Smaldone GC. Albuterol delivery in a model of mechanical ventilation: comparison of metered-dose inhaler and nebulizer efficiency. Am J Respir Crit Care Med 1995;152(4 Pt 1): 1391–1394.
25. Mouloudi E, Katsanoulas K, Anastasaki M, Askitpoulou E, Georgopoulos D. Bronchodilator delivery by metered-dose inhaler in mechanically ventilated COPD patients: influence of end-inspiratory pause. Eur Respir J 1998;12(1):165–169.
26. Craven DE, Kunches LM, Kilinsky V, Lichtenberg DA, Make BJ, McCabe WR. Risk factors for pneumonia and fatality in patients receiving continuous mechanical ventilation. Am Rev Respir Dis 1986;133(5):792–796.
27. O'Riordan TG, Palmer LB, Smaldone GC. Aerosol deposition in mechanically ventilated patients: optimizing nebulizer delivery. Am J Respir Crit Care Med 1994;149(1):214–219.
28. O'Doherty MJ, Thomas SHL, Page CJ, Treacher DF, Nunan TO. Delivery of a nebulized aerosol to a lung model during mechanical ventilation: effect of ventilator settings and nebulizer type, position, and volume of fill. Am Rev Respir Dis 1992;146(2):383–388.
29. Fink JB, Dhand R, Grychowski J, Fahey PJ, Tobin MJ. Reconciling in vitro and in vivo measurements of aerosol delivery from a metered-dose inhaler during mechanical ventilation and defining efficiency-enhancing factors. Am J Respir Crit Care Med 1999;159(1): 63–68.
30. Hughes JM, Saez BS. Effects of nebulizer mode and position in a mechanical ventilator circuit on dose efficiency. Respir Care 1987; 32(12):1131–1135.

Foreword

New Horizons In Respiratory Care: The Pharmacology of Inhaled Aerosol Drug Therapy

James B Fink MS RRT FAARC and Joseph L Rau PhD RRT FAARC

In December of 1999, the 45th International Respiratory Congress of the American Association for Respiratory Care devoted the New Horizons Symposium to an examination of inhaled aerosol drug therapy both for treatment of the respiratory tract and for potential systemic therapy. The rationale for choosing to examine the clinical pharmacology of inhaled aerosol drugs derives from important advances in drug availability and the science of aerosol delivery, with concomitant advances in the understanding of drug actions and their clinical applications.

The inhalation of aerosolized drugs for therapeutic purposes is not a novel form of treatment in lung disease. The inhalation of fumes from *datura* plant species for respiratory disorders dates at least to 2000 BC in India.[1] The use of nebulized drug therapy can be dated to the invention of the atomizer by Euget-les-Bains in 1849. Development of the metered-dose inhaler (MDI) began in 1955, following a suggestion from Susie, the 13-year-old asthmatic daughter of Dr George Maison, then President of Riker Labs (now 3M Pharmaceuticals), and this revolutionary, convenient inhalation device was marketed in 1956, following United States Food and Drug Administration approval.[2]

A milestone in the clinical use of aerosolized drug therapy occurred in 1974, with the Conference on the Scientific Basis of Respiratory Therapy, held on May 2–4, 1974, at the Temple University Conference Center at Sugarloaf. The "Sugarloaf Conference" as it came to be known, brought together well-known investigators in pulmonary medicine to examine the scientific basis of respiratory care. The conference comprehensively reviewed respiratory care at the time, including a section devoted to aerosol therapy. The recommendations for further study of aerosol therapy included:[3]

- Studies to determine regional deposition of nonhygroscopic stable aerosols
- Studies on the effect of water vapor in patients with chronic obstructive pulmonary disease
- Studies on the physicochemical properties of bronchial secretions
- Studies with bronchodilators
- Studies with corticosteroids

In the 1980s and 1990s, the development and delivery of aerosol drug formulations began to increase in sophistication and to be put on a firm scientific footing. In 1981, Newman et al found decreased oropharyngeal loss of inhaled drug with the addition of an extension tube or reservoir device to an MDI.[4] Use of add-on devices (as spacers and holding chambers came to be termed) also helped remove hand-breath coordination problems often seen with MDIs. An early reservoir device, the InspirEase, was described by Tobin et al in 1982, and incorporated features such as a flow signal indicator and small storage size.[5] In 1983, Dolovich et al described similarly reduced oropharyngeal loss with the AeroChamber, a true holding chamber with a one-way inspiratory valve, flow signal, and flexible opening for the entire MDI canister and mouthpiece actuator.[6] An alternative aerosol inhalation device, the dry powder inhaler, became available in the United States in the early 1970s for delivery of cromolyn sodium (SpinHaler). Other dry powder inhaler devices have followed, culminating in the more sophisticated Turbuhaler and Diskus.

The use of inhaled drug therapy in pulmonary disease represents the intersection of pharmacology, aerosol science, and clinical medicine. Borgström noted that the drug cannot be considered separately from the aerosol delivery system:

> Each combination of active drug and device is a unique pharmaceutical formulation, as both the drug itself and the device can influence the overall properties of the formulation.[7]

The implication of this view is that one size (aerosol device) does not fit all (drugs or formulations). Placing the

drug/delivery system unit into the context of pharmacology leads to consideration of the disposition of inhaled drugs in the body as a whole. In this 15th Annual New Horizons Symposium, we continue the tradition of examining and updating the science of aerosolized drug therapy, exemplified in the 1974 Sugarloaf Conference. The authors herein present a digest of current information for practicing clinicians, to provide understanding of inhaled medications in a comprehensive way, based on their pharmacology, aerosol delivery system, and clinical effects. A logical beginning for discussing aerosolized drugs is the pharmacokinetics of inhaled aerosol agents delivered to the lungs, presented by Theodore Witek. Thomas O'Riordan presents a review of the continually developing class of anti-infective drugs for pulmonary infections. Developments in the traditional drug classes of inhaled corticosteroids and β agonist bronchodilators are reviewed by Gene Colice and Joseph Rau, respectively. An alternative bronchodilator class, the anticholinergic agents, are presented by Sammy Campbell. Bruce Rubin considers the extensive investigations into the nature of respiratory tract secretions and inhaled agents that can benefit patients with abnormal secretions. Kevin Corkery discusses inhaled drugs used for systemic therapy, with the lung offering a potential gateway to the entire body. The development of and improvements in delivery devices for inhaled aerosols are addressed by James Fink, in a forward-oriented review, perhaps better termed a "preview."

We currently have more inhaled drugs and a greater variety of aerosol delivery devices than at any other time in the 50-year history of respiratory care as a separate health care discipline. This special issue of the journal presents a timely update on aerosolized drug therapy for the practicing clinician. It is hoped that this will be the first of many future symposia providing a convenient synthesis of the current scientific basis of aerosolized drug therapy.

James B Fink MS RRT FAARC
Division of Pulmonary and Critical Care Medicine
Loyola University of Chicago Stritch
School of Medicine
Hines Veterans Hospital
Hines, Illinois
AeroGen
Sunnyvale, California

Joseph L Rau PhD RRT FAARC
Department of Cardiopulmonary Care Sciences
College of Health and Human Services
Georgia State University
Atlanta, Georgia

Guest Co-Editors

REFERENCES

1. Gandevia B. Historical review of the use of parasympatholytic agents in the treatment of respiratory disorders. Postgrad Med J 1975:51(7 Suppl):13–20.
2. Freedman T. Medihaler therapy for bronchial asthma: a new type of aerosol therapy. Postgrad Med 1956;20:667–673.
3. Conference on the scientific basis of respiratory therapy. Final reports: summaries and recommendations. Aerosol therapy. Am Rev Respir Dis 1974;110(6 Pt 2):7–9.
4. Newman SP, Morén F, Pavia D, Little F, Clarke SW. Deposition of pressurized suspension aerosols inhaled through extension devices. Am Rev Respir Dis 1981;124(3):317–320.
5. Tobin MJ, Jenouri G, Danta I, Kim C, Watson H, Sackner MA. Response to bronchodilator drug administration by a new reservoir aerosol delivery system and a review of other auxiliary delivery systems. Am Rev Respir Dis 1982:126(4):670–675.
6. Dolovich M, Ruffin R, Corr D, Newhouse MT. Clinical evaluation of a simple demand inhalation MDI aerosol delivery device. Chest 1983;84(1):36–41.
7. Borgström L. Local versus total systemic bioavailability as a means to compare different inhaled formulations of the same substance. J Aerosol Med 1998;11(1):55–63.

The Fate of Inhaled Drugs: The Pharmacokinetics and Pharmacodynamics of Drugs Administered by Aerosol

Theodore J Witek Jr DrPH RRT RPFT

Introduction
Why Inhale?
Inhaled Albuterol: Getting Drug to the Site of Action
Optimizing Inhalation Therapy: Pulmonary Targeting of Inhaled Corticosteroids
Predicting Pharmacodynamic Effects from Pharmacokinetics: Tiotropium
Summary

[Respir Care 2000;45(7):826–830] *Key words: aerosols, inhalation therapy, pharmacokinetics, albuterol, inhaled corticosteroids, tiotropium.*

Introduction

The respiratory therapist is often responsible for recommending an aerosol generator for delivery of a therapeutic agent, ensuring its proper administrations, and monitoring the response. There are important physical and biologic events that occur between the time of administration of an aerosol and an observed clinical response (eg, improved air flow, tachycardia). Though a sufficient amount of drug targeted for the lung will usually get there and remain there for its intended pulmonary response, a portion of it will probably be absorbed into the systemic circulation, where it will be distributed in the body, often to undergo some degree of metabolism, and ultimately to be excreted (unchanged or metabolized). These events (ie, what the body does to the drug) can collectively be referred to as pharmacokinetics. The observed clinical response (ie, what the drug does to the body) is referred to as pharmacodynamics.[1]

In this brief review, some key aspects of the relationship between pharmacokinetics and pharmacodynamics for inhaled drugs will be discussed through examples from the literature, using 3 classes of inhaled drugs to illustrate principles. First, the ability to broaden the therapeutic window via inhaled delivery will be described for albuterol, along with methods to evaluate its relative lung bioavailability. Second, the specific pulmonary targeting (ie, topical to systemic effects) of inhaled corticosteroids (ICS) will be reviewed as an example of how both pharmacokinetic properties and delivery technique can impact optimal therapeutic effect. Finally, a review of how one might predict lung to systemic effects from basic pharmacologic and pharmacokinetic information will be reviewed for the experimental long-acting anticholinergic agent tiotropium.

Why Inhale?

The intended site of action of respiratory therapeutic aerosols is the lung. When utilizing aerosols for respiratory therapy, however, isolating the delivery of the drug to the lung itself (vs, for example, to the oropharynx) will most often optimize its therapeutic window, ie, the difference between a drug's therapeutic benefit (eg, bronchodilation) and its unwanted effects (eg, tachycardia). The inhaled route for respiratory therapeutics is seen as advantageous in that drug is delivered directly to the site of action and that lower doses can be administered relative to parenteral or oral preparations.[2] These features, in turn, can broaden the therapeutic window by achieving optimal efficiency and minimizing adverse effects.

Inhaled Albuterol: Getting Drug to the Site of Action

The concept described above was nicely illustrated in a study by Lipworth et al,[3] in which a group of asthmatics received salbutamol either orally (2 mg), sublingually (2 mg), or via metered-dose inhaler (MDI) (0.2 mg), with subsequent monitoring of pharmacokinetic and pharmaco-

Theodore J Witek Jr DrPH RRT RPFT is affiliated with the Department of Respiratory/Immunology, Boehringer Ingelheim Pharmaceuticals, Ridgefield, Connecticut.

Correspondence: Theodore J Witek Jr DrPH RRT RPFT, Department of Respiratory/Immunology, Boehringer Ingelheim Pharmaceuticals, 900 Ridgebury Road/P.O. Box 368, Ridgefield CT 06877-0368. E-mail: twitek@rdg.boehringer-ingelheim.com.

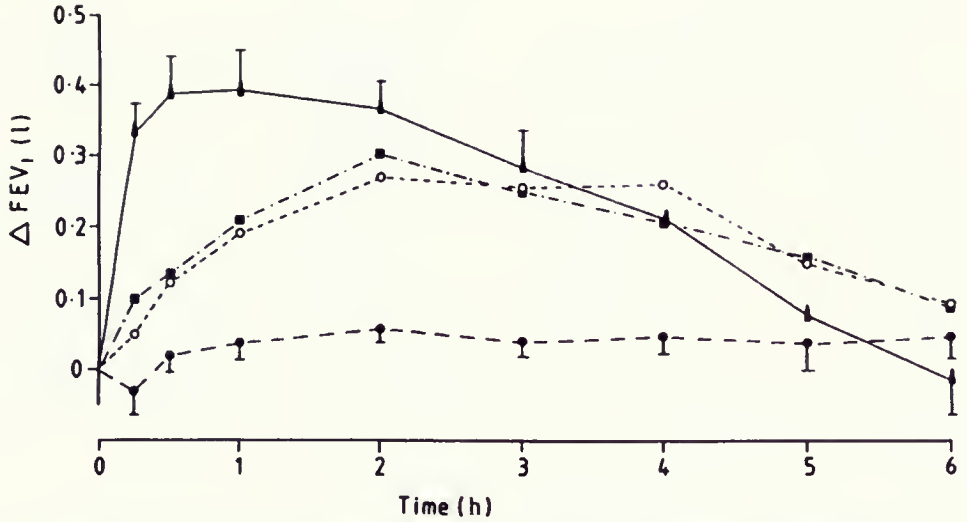


Fig. 1. Change from baseline in forced expiratory volume in the first second (FEV_1) in 7 asthmatic patients given placebo (closed circles), 200 μg metered-dose inhaled salbutamol (triangles), oral salbutamol 2 mg tablet (squares), or sublingual salbutamol 2 mg tablet (open circles). Values are means. For clarity, standard error bars are only shown for placebo and inhaled salbutamol. (From Reference 3, with permission.)

dynamic end points. For lung function (Fig. 1), forced expiratory volume in the first second (FEV_1) was improved relative to placebo for all routes of administration, with the response following inhalation significantly greater than that following oral or sublingual administration. The time to peak response was also earlier following inhalation (30 min) than with oral or sublingual administration (2 h). The unintended pharmacodynamic response of tremor was also evaluated. Here, an increase in tremor response was confined to the oral and sublingual routes (Fig. 2). Therefore, the improved therapeutic window with inhalation was clearly demonstrated. This report confined pharmacokinetic analysis to the oral and sublingual routes and noted similar profiles, with the exception of an initial delayed absorption following sublingual administration. This is suggestive of minimal buccal absorption, with the systemic levels coming from gut absorption following swallowing of the dissolving sublingual tablet.

Though the above example clearly points to different effects following oral versus inhaled salbutamol, it is also interesting to consider the fate of the inhaled drug itself and methods to determine the relative bioavailability of such drugs to the lungs.

Inhaled therapy, while remaining the optimal choice for many drug classes, is inefficient. That is, only a small fraction of the drug that leaves the aerosol generator actually is deposited in and available to the lung. Despite this inefficiency, the lung-to-systemic effects remain favorable. Methods used to quantify the fate of administrated aerosols include radiolabeled aerosol studies, charcoal ingestion methods, and timed urinary excretion surrogates of lung bioavailability.

In the aerosol deposition studies, radiolabeled particles are inhaled, followed by gamma scintigraphy to follow the fate of particles. Among the classic studies reported by Newman et al include the observation that only some 10% of radiolabeled aerosol of Teflon reaches the lung, with the remainder swallowed.[4]

In the charcoal technique, inhaled drug is simultaneously administrated with charcoal, which blocks oral absorption, leaving the recovered fraction attributable to the lung delivery. With this technique, Borgström and Nilsson[5] reported a lung bioavailability of approximately 10%.

The relative bioavailability of inhaled salbutamol to the lung evaluated by measuring early urinary excretion also serves to illustrate some important pharmacokinetic principles of inhaled drugs. In their simple technique, Hindle and Chrystyn[6] took advantage of the biphasic renal excretion following inhaled salbutamol. The initial elimination (ie, 30 min) represents the fraction of dose administrated to the lungs, rapidly absorbed via the alveoli, then excreted unchanged by the kidneys. The second phase represents the dose swallowed after impaction in the oropharynx. To support this theory, they showed (Fig. 3) that little drug is excreted in urine 30 minutes after oral ingestion because of the lag time between administration and start of absorption. The urine drug recovery 30 minutes after inhalation, in contrast, was significantly greater. This method was subsequently validated in practice, where 30-minute urine recovery of salbutamol was measured following a variety of inhalation techniques.[7] For example, they observed significantly greater elimination in the first 30 minutes when drug was inhaled slowly (10 L/min) versus quickly (50 L/min) and with breath-holding (10 s) versus without breath-holding. Thus, the fate of the inhaled salbu-

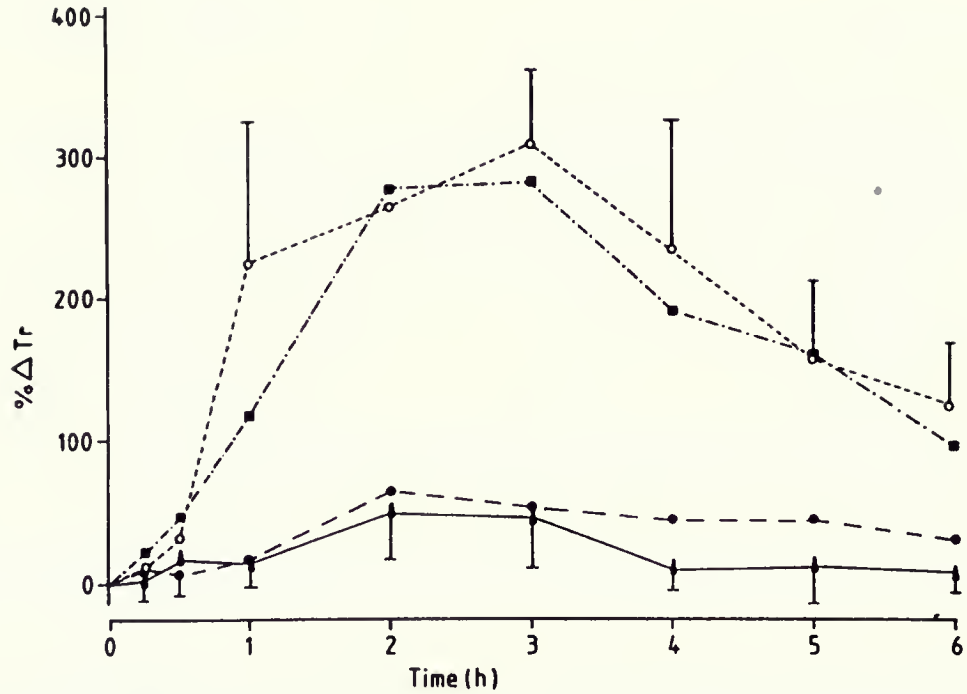


Fig. 2. Tremor response (as percentage change) to placebo (closed circles), inhaled salbutamol (triangles), oral salbutamol (squares), and sublingual salbutamol (open circles). For clarity, standard error bars are only shown for placebo and sublingual salbutamol. (From Reference 3, with permission.)

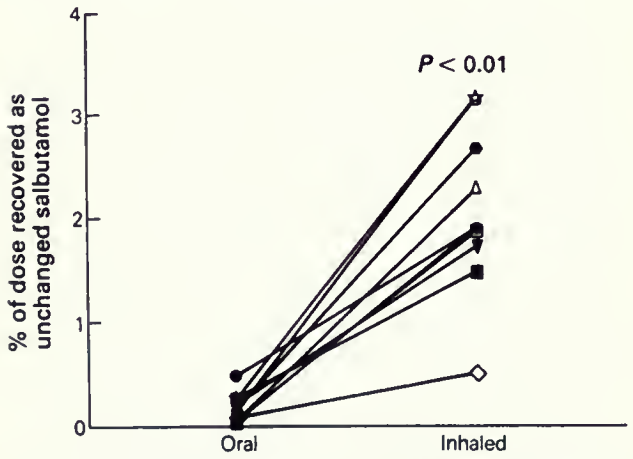


Fig. 3. Individual values of urinary unchanged salbutamol recovery 0.5 hour after oral and inhaled administration. (From Reference 6, with permission).

tamol as measured by its excretion in the urine allowed for the evaluation of aerosol administration techniques.

Optimizing Inhalation Therapy: Pulmonary Targeting of Inhaled Corticosteroids

As seen with the previous example of salbutamol, the route of administration impacts the therapeutic index. Differences in the therapeutic index can also manifest within a given route of administration. This is particularly true for inhaled therapy, with several illustrative and relevant examples coming from the clinical investigations of inhaled corticosteroids. Specifically, different formulations and different delivery devices can produce meaningful differences in topical activity by affecting the dose deposited in the lung and, for drugs absorbed orally, by affecting the amount of drug deposited in the oropharynx and subsequently swallowed.

The primary goal in optimizing the therapeutic window of an ICS is to maximize its action in lung tissue while minimizing systemic exposure that primarily leads to adverse effects. In maximizing therapeutic effect, the potency of a given ICS (related to steroid receptor binding affinity) and the amount of drug reaching the lung are important factors.[8] In the broad sense, efficacy relates to the molecular and cellular activity that reduces airway inflammation and airway hyperresponsiveness. Clinically, the effects translate into improved symptoms, reduced need for oral steroids, and general improvement in lung function.[9]

The goal to minimize systemic exposure is embedded in avoiding clinically problematic effects, including hypothalamic-pituitary-adrenal axis suppression, inhibition of bone formation and growth, and a variety of other metabolic, hematologic, and central nervous system effects. In setting the safety threshold of an ICS, the amount of drug

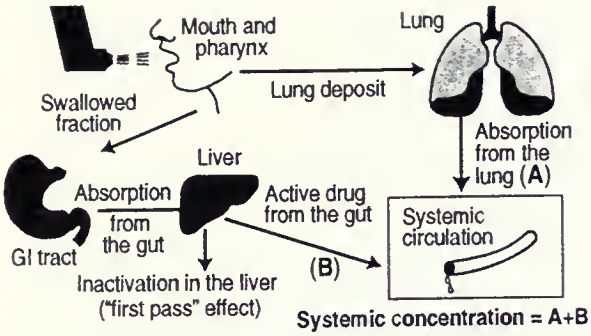


Fig. 4. Systemic concentration of inhaled corticosteroids is determined by oral bioavailability of swallowed fraction and by absorption from lung (inhaled fraction). (From References 8 and 9, with permission.)

that becomes available in the systemic circulation is a primary concern.

The key concepts in determining the therapeutic window of an ICS are best understood by understanding the potential fate of an ICS following administration. As illustrated in Figure 4, therapeutics aim at optimizing effect in the lung while minimizing systemic concentration. Important pharmacokinetic properties of a drug that would foster a wider therapeutic index include slow absorption from the lung, low oral bioavailability, and rapid systemic clearance.[8]

First, prolonged exposure of an ICS in the lung itself may enhance the local anti-inflammatory effect. A surrogate of pulmonary retention can be evaluated by monitoring the differences between drug half-life following inhalation and intravenous administration. Here, a longer half-life after inhaled delivery would indicate that the rate of pulmonary absorption limits the ultimate excretion from the body. Second, low oral bioavailability, or the fraction of ingested dose that reaches the systemic circulation, is affected by physiologic effects of gastrointestinal absorption and inactivation by "first pass" metabolism in the liver. More importantly, however, there are several important factors in the hands of the practitioner that can minimize systemic effects by minimizing the amount of drug that reaches the gastrointestinal tract. These include selection of a device that minimizes oropharyngeal deposition, utilizing a spacer device, and mouth rinsing and expectoration after treatment. The impact of such interventions was illustrated by Selroos and Halme,[10] who reported a difference in the pharmacodynamic systemic measure of serum cortisol following budesonide when the drug administration was followed by mouth rinsing or not (Table 1). This illustrates the potential impact of aerosol administration techniques on the subsequent pharmacokinetic (reduce oral bioavailability) and pharmacodynamic (reduce serum cortisol) response.

Table 1. Serum Cortisol Following Budesonide Inhalation With and Without Mouth Rinsing

Drug and Dose	Mouth Rinse	Serum Cortisol (nmol/l)
Budesonide 1.6 mg	Yes	440 ± 63
Budesonide 1.6 mg	No	375 ± 56
Difference		65 ± 58*

Values are mean ± SD.
*p = 0.007.

Predicting Pharmacodynamic Effects from Pharmacokinetics: Tiotropium

Tiotropium is an experimental anticholinergic agent that is being developed as a once-daily inhaled bronchodilator.[11] It's long duration of action is best explained by its prolonged binding to muscarinic receptors. For example, the half-lives of the drug-receptor complex at the M3 receptor (responsible for airway smooth muscle relaxation) is orders of magnitude longer for tiotropium (34.7 ± 2.9 h) than for ipratropium (0.26 ± 0.02 h).[12]

In a discussion of the relationship between predicted lung and systemic levels of drug, Disse et al[13] used basic pharmacologic principles to predict local concentrations and their impact on receptor binding and potential response in humans. This approach addressed the following questions.

What are the relative amounts in the lung versus systemic circulation?

As a quaternary ammonium compound, tiotropium has a positive charge and would be expected to have minimal systemic absorption following inhalation. In patients, plasma levels are indeed low, at approximately 2 pg/mL at trough (ie, before dosing), with transient postinhalation peaks measured at approximately 14 pg/mL.[13] Such concentrations correspond to approximately 4.2 pM and 30 pM, respectively.

In order to predict tiotropium concentrations in the lung's epithelial lining fluid, estimations were made by assuming that 4 μg of the inhaled 20 μg dose (20%) is contained in fine particles likely to reach the lung. Again, assuming a volume of epithelial lining fluid of 20 mL, a tiotropium concentration of approximately 2 μM would be estimated.

What impact do these concentrations have on receptor binding?

From classic pharmacology, receptor occupancy can be estimated as a function of drug concentration based on the following:

$$[RD]/[Rt] = [D]/(K_D + [D])$$

where [RD] is the concentration of drug-receptor complex, [Rt] is the total number of receptors, and [D] is the concentration of free drug. [RD]/[Rt] reflects the proportion of occupied receptors. K_D is the equilibrium dissociation constant for the drug-receptor complex. A kinetically determined K_D of 14 pM has been established for tiotropium.

Given this, one could predict, assuming an equilibrium state, that less than one quarter of systemic receptors would be occupied. The value is probably less, as a true equilibrium state is probably not reached. Near full receptor occupancy would require much higher concentrations, such as those estimated for the lungs. Thus, this approach gives an appreciation for what might be predicted for lung and systemic responses, namely, a good therapeutic effect in the airway, with minimal systemic adverse effects.

What might be the impact of these estimations?

It has been postulated that, given the high post-junctional neurotransmitter tonus, acetylcholine is still likely to elicit a near full cholinergic response if < 50% of receptors are occupied by an antagonist such as tiotropium. Thus, one can predict minimal systemic effects. In the lung, however, much higher topical levels lead to near full receptor occupancy and thus probably explain the long duration of bronchodilation[14,15] and bronchoprotective[16] effects. These differences are important in the ultimate determination of a drug's therapeutic index (ie, its safety to efficacy or risk to benefit). This will ultimately be confirmed or refuted in long-term clinical trials.

Summary

Prior to a drug achieving its effects (ie, pharmacodynamics), there are numerous events within the body that determine its ultimate fate. The effects of the "body on the drug" has been referred to as pharmacokinetics—how the favorable lung-to-systemic effects predicted from this exercise translate into practice.

Inhaled drugs have enjoyed the major feature of having "local" effects on the target organ of the lung. Broadly, lower doses can be used and adverse effects are often less than with oral or parenteral administration. Nevertheless, key features of respiratory drugs and their administration can impact their fate and ultimate utility. This review has provided some relevant examples of basic pharmacokinetics principles as related to inhaled products, with emphasis on those factors that help to partition lung-to-systemic effects.

REFERENCES

1. Benet LZ, Mitchell JR, Sheiner LB. General principles. In: Gilman AG, Rall TW, Nies AS, Taylor P, editors. Goodman and Gilman's the pharmacological basis of therapeutics, 8th ed. New York: Persamon Press; 1990: 1–2.
2. Witek TJ, Schachter EN. Respiratory care pharmacology and therapeutics. Philadelphia: WB Saunders; 1994.
3. Lipworth BJ, Clark RA, Dhillon DP, Moreland TA, Struthers AD, Clark GA, McDevitt DG. Pharmacokinetics, efficacy and adverse effects of sublingual salbutamol in patients with asthma. Eur J Clin Pharmacol 1989;37(6):567–571.
4. Newman SP, Pavia D, Moren F, Sheahan NF, Clarke SW. Deposition of pressurised aerosols in the human respiratory tract. Thorax 1981;36(1):52–55.
5. Borgström L, Nilsson M. A method for determination of the absolute pulmonary bioavailability of inhaled drugs: terbutaline. Pharm Res 1990;7(10):1068–1070.
6. Hindle M, Chrystyn H. Determination of the relative bioavailability of salbutamol to the lung following inhaltion. Br J Clin Pharmacol 1992;34(4):311–315.
7. Hindle M, Newton DAG, Chrystyn H. Investigations of an optimal inhaler technique with the use of urinary salbutamol excretion as a measure of relative bioavailability to the lung. Thorax 1993;48(6): 607–610.
8. Kelly HW. Establishing a therapeutic index for the inhaled corticosteroids. Part I. Pharmacokinetic/pharmacodynamic comparison of the inhaled corticosteroids (review). J Allergy Clin Immunol 1998: 102(4 Pt 2):S36–S51.
9. Barnes PJ. Inhaled glucocorticoids for asthma (review). N Engl J Med 1995;332(13):868–875.
10. Selroos O, Halme M. Effect of a Volumatic spacer and mouth rising on systemic absorption of inhaled corticosteroids from a metered dose inhaler and dry powder inhaler. Thorax 1991;46(12):891–894.
11. Witek TJ, Souhrada JF, Serby CW, Disse B. Tiotropium (Ba679): pharmacology and early clinical observations. In: Spector SS, editor. Anticholinergic agents in the upper and lower airways. New York: Marcel Dekker; 1999: 137–152.
12. Disse B, Reichel R, Speck G, Traunecker W, Ludwig Rominger KL, Hammer R. Ba679BR, a novel long acting anticholinergic bronchodilator. Life Sci 1993;52(5–6):537–544.
13. Disse B, Speck G, Rominger KL, Witek TJ Jr, Hammer R. Tiotropium (Spiriva): mechanistical considerations and clinical profile in obstrutive lung disease (review). Life Sci 1999;64(6–7):457–464.
14. Maesen FPV, Smeets JJ, Costongs MAL, Wald FDM, Cornelissen PJG. BA 679BR, a new long-acting antimuscarinic bronchodilator: a pilot dose-escalation study in COPD. Eur Respir J 1993;6(7):1031–1036.
15. Littner MR, Howitt JS, Tashkin DP, Friedman M, Serby CW, Menjoge SS, Witek TJ. Long-acting bronchodilation with once-daily dosing of tiotropium (Spiriva) in stable chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2000;161(4 Pt 1):1136–1142.
16. O'Connor BJ, Towse LJ, Barnes PJ. Prolonged effect of tiotropium bromide on methacholine-induced bronchoconstriction in asthma. Am J Respir Crit Care Med 1996;154(4 Pt 1):876–880.

Inhalable Drugs for Systemic Therapy

Kevin Corkery RRT

Introduction
Problems in Drug Delivery of Macromolecules
Suitability of the Lung Periphery for Systemic Drug Delivery
First-Generation Aerosol Devices
The Delivery Device and Lung Periphery Deposition
The Inhalable Drug Industry Today
The Future of Inhalable Therapeutics
Summary
[Respir Care 2000;45(7):831–835] *Key words: aerosol, inhalable, systemic, peptides, macromolecule, nebulizer, metered-dose inhaler.*

Introduction

Aerosol systems, such as metered-dose inhalers, dry powder inhalers, and liquid jet or ultrasonic nebulizers for delivery of bronchodilators and inhalable corticosteroids to treat asthma or chronic obstructive pulmonary disease have existed for many years, and have proven effective in delivering drug to the airways for pulmonary applications. More recently, however, there has been substantial interest in using the lung, and in particular the alveolar surface, as a portal to the systemic circulation for macromolecules such as proteins and peptides, which otherwise must be given by injection.

Problems in Drug Delivery of Macromolecules

Because of their size and delicacy, peptides, proteins, and other macromolecules have traditionally been systemically administered via injection. But there are problems with administering them this way. Most patients do not like the pain and inconvenience of injection, particularly when required repeatedly for the treatment of chronic disease such as diabetes or multiple sclerosis. This dislike can result in poor patient compliance and inadequate disease management.[1] With the development of more long-term and frequently administered injection drugs (eg, growth factors, anti-infectives, and other chronic disease treatments) the pharmaceutical industry has increasingly sought noninvasive alternatives to needle injection.

To date, however, traditional noninvasive delivery systems have not proved effective for macromolecules. Pills, tablets, and oral solutions are unsuitable because of poor absorption or inactivation by gastric juices and digestive enzymes. Transdermal delivery systems are also inadequate because of the size constraints of macromolecules or other inherent physical properties that prevent them from crossing skin layers without the addition of irritating enhancers. Research has also shown that the nasal route has low natural bioavailability and high variability for proteins and peptides.[2] The natural bioavailability of macromolecules (eg, insulin and growth hormone) when delivered nasally is generally $< 2\%$. To achieve higher system efficiency and greater bioavailability, penetration enhancers are required that can cause local irritation and long-term mucosal injury.

Suitability of the Lung Periphery for Systemic Drug Delivery

The biology of the lung makes it suitable for systemic drug delivery. Many proteins and peptides are absorbed through the alveoli into the bloodstream naturally, with high drug absorption and without the need for enhancers used for other noninvasive routes.[3] This high bioavailabil-

Kevin Corkery RRT is affiliated with Inhale Therapeutic Systems, San Carlos, California.

A version of this paper was presented by Mr Corkery during the New Horizons Symposium, "Clinical Pharmacology of Inhaled Agents for the Respiratory Care Clinician," at the American Association for Respiratory Care's 45th International Respiratory Congress, December 14, 1999, in Las Vegas, Nevada.

Correspondence: Kevin Corkery RRT, Inhale Therapeutic Systems, 150 Industrial Road, San Carlos CA 94070. E-mail: kcorkery@inhale.com.

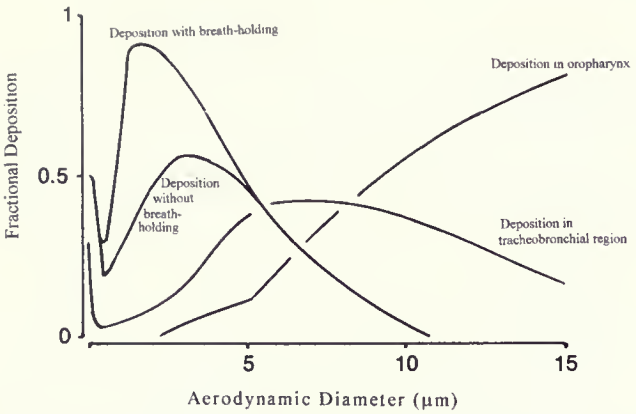


Fig. 1. Pulmonary deposition as a function of particle size, with inspiratory flow of 22.5 L/min. Fractional deposition curves for oropharynx and tracheobronchial region differed insignificantly with and without breath-holding. (Redrawn, using data from Reference 12.)

ity makes the lung a natural target for peptides and proteins. In addition, the lung is a robust organ, able to handle about 30 mg per day of inhaled nuisance dusts day after day for years without deleterious effect.[4] This combination of the bioavailability of peptides and proteins when delivered via the lung and the robustness of the lung itself make the lung periphery a logical target for drug delivery.[5–10]

On inhalation, air passes through the trachea, which branches more than 22 times into successively smaller airways that constitute the bronchial network, eventually reaching the grapelike clusters of the alveoli. Each breath of air is distributed deep into the lung tissue, to the alveolar epithelium, the surface area of which measures approximately 80–100 m^2 in humans. This large surface has about half a billion alveoli through which oxygen passes into the bloodstream via an extensive capillary network. Large-molecule drugs such as peptides and proteins do not easily pass through the airway surface (which has a total surface area of about 3.0 m^2) because it is lined with a thick, ciliated, mucus-covered cell layer, making it nearly impermeable. But these large molecules do permeate the alveoli, which have a thin, single-cellular layer, enabling absorption into the bloodstream. Because the alveoli reside beyond the terminal branches of the airway, any pulmonary approach to delivering drugs for systemic disease must target the lung periphery.

To reach the lung periphery, a drug must be delivered in particles of 1–3 μm (optimal size $\leq$ 2 μm) with slow, deep inhalation.[11] Particles $>$ 10 μm tend to be swallowed, and 6–10 μm particles deposit in the airways (Figure 1).[11,12]

First-Generation Aerosol Devices

Until recently, pulmonary drug delivery systems were capable of dispensing drug to the airway only for local application, such as in asthma. Metered-dose inhalers, breath-activated dry powder inhalers, and liquid jet and ultrasonic nebulizers are useful in the management of asthma, but such devices were not designed to deliver drugs into the lung periphery. They have been primarily designed to deliver potent drugs such as corticosteroids and bronchodilators, both of which are bioactive in the lung at 5–20 μg per dose.[13] Dose reproducibility is most often inconsistent, varying per puff, which is acceptable when the therapeutic window is large, as is true with these potent drugs. However, when the therapeutic window is narrow, as is true with most protein drugs, dose reproducibility is required. These systems have not been able to deliver most macromolecules, which need to be delivered to the lung periphery at doses of 2–20 mg,[12] because of the devices' low system efficiency, low drug mass (also known as "payload") per puff, poor formulation stability for macromolecules, and poor dosing reproducibility.[14]

To effectively deliver macromolecules to the lung periphery in therapeutic doses, 5 basic criteria must be met.

- The system must provide efficient delivery of the drug to the lung periphery. This requires formulating the drug so that it is deliverable in a cloud containing particles of 1–3 μm (optimal size $\leq$ 2 μm) with slow, deep inhalation. (Some aerosol systems can deliver only 10–12% of the dispensed drug in the correct particle size for lung deposition.)[13] It also requires designing the delivery device so that the aerosol generated easily reaches the alveolar region with a minimum of patient effort and with minimal oropharyngeal impaction (which causes the medication to be swallowed rather than inhaled).
- The therapeutic drug dose must be reproducible from dose to dose. Package inserts for these products will present this in terms of *nominal* or *dispensed* dose (ie, the amount of drug in the unit dose blister package or ampule) and *delivered* dose (ie, the amount of drug in the dose that is bioavailable).
- The system should accommodate flexible dosing, because patients may require different doses at different times.
- The delivery device must be portable and easy to use to optimize patient compliance and disease management.
- The drug formulation must be stable at room temperature. This too improves portability and convenience of using the system.

The Delivery Device and Lung Periphery Deposition

Fine powder particles adhere to each other (agglomerate) and can be difficult to break apart into respirable particles that can be slowly inhaled. Breath-activated powder inhalers for asthmatics are designed to use the force generated by fast inspiration to break apart powder clumps. Unfortunately, there is not enough energy in a human inhalation to efficiently break apart very fine powder

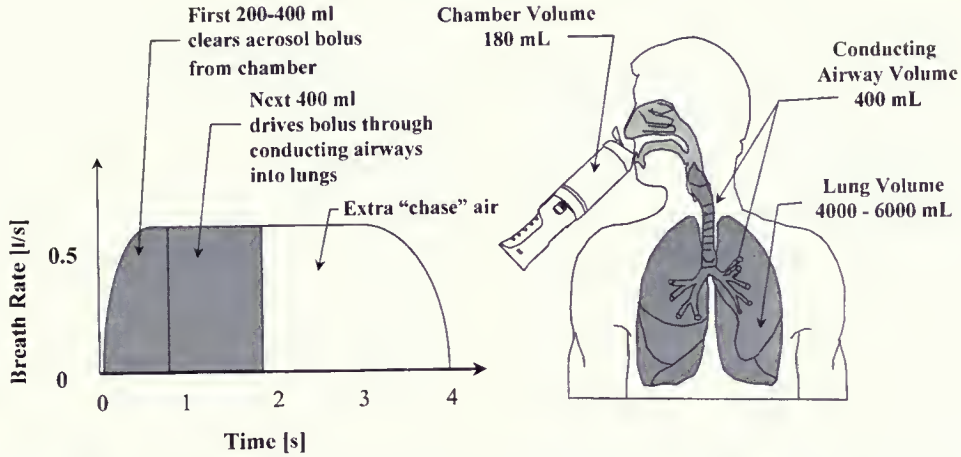


Fig. 2. With the Innova durable dry powder delivery device (made by Inhale Therapeutic Systems), the patient slowly inhales a puff of medicine through the device mouthpiece, receiving the medicine first, followed by a much larger volume of air that pushes the drug plume down into the alveoli. (Figure courtesy of Inhale Therapeutic Systems.)

clumps, and the harder the inhalation, the faster the particles move, increasing dosing variability and the tendency of particles to impact in the mouth and throat.

The Innova device technology (Inhale Therapeutic Systems) separates the patient's breathing maneuver from the generation of the aerosol by using compressed air to deagglomerate the powder particles and deliver the aerosol plume into a clear plastic holding chamber, eliminating the need for coordination of aerosol generation and inhalation. The patient inhales the cloud with the slow, deep inspiration that optimizes alveolar deposition. Because the chamber is transparent, the patient knows immediately whether a full dose of medicine has been inhaled. The device delivers the medicine early in the inspiration, followed by a much larger volume of air that pushes the drug down into the alveoli (Fig. 2). The device requires no power source, contains no batteries or chips, and is easily cleaned.

The Inhalable Drug Industry Today

Currently, at least 5 companies are working on the development of inhalable proteins:

- AeroGen (AeroDose inhaler system)
- Alkermes (AIR technology)
- Aradigm Corporation (AERx pulmonary drug delivery system)
- Dura Pharmaceuticals (Spiros pulmonary drug delivery system)
- Inhale Therapeutic Systems (Inhance drug delivery platform)

AeroGen (Sunnyvale, California)

AeroGen's AeroDose inhaler system is designed to enable aerosolization of small or large molecules in liquid solution or suspension formulations. The technology uses the vibration of a curved metal plate that contains preformed holes of a predetermined size to generate the aerosol. The device's metering valves allow flexibility in dosing. Electronic controls enable breath actuation of drug delivery and control of aerosol flow and inspiratory flow. Delivery of a single dose of drug is accomplished with single or multiple breaths.

Alkermes (Cambridge, Massachusetts)

Alkermes's AIR technology employs dry powder delivery of small-molecule, protein, and peptide drug particles to the deep lung. The delivery device is breath-activated, requiring no additional power source. Particles are produced in a one-step spray-drying process that uses only small quantities of excipients while accommodating large concentrations of drug, if needed. Its dry powder technology, according to Alkermes, has the potential for prolonged drug release. To date, the company has 3 major pharmaceutical partners and 5 drugs (proteins and small molecules) in large animal or human clinical trials.

Aradigm Corporation (Hayward, California)

The AERx pulmonary drug delivery system uses proprietary technology to create aerosols from liquid drug formulations and to deliver these aerosols locally to the lungs or systemically via the lungs. The delivery device, which depends on the patient's active breath control, has data capture abilities, enabling health care professionals to download and analyze data for patient compliance. The company has several drugs in preclinical or clinical trials, including morphine (phase 2), insulin, (phase 2), and dornase alfa (preclinical).

Dura Pharmaceuticals (San Diego, California)

Dura's Spiros pulmonary drug delivery system aerosolizes pharmaceuticals in a powder formulation for pulmonary delivery. The system comprises a battery-operated electromechanical inhaler and a multi-dose cassette or blisterdisk powdered-drug storage unit. The company primarily focuses on developing inhalable steroids for asthma treatment but is interested in proteins and other macromolecules as well.

Inhale Therapeutic Systems (San Carlos, California)

Inhale Therapeutic Systems focuses on its Inhance dry powder technology platform for lung periphery aerosol delivery of drugs. The Inhance drug delivery platform combines multiple powder and device technologies for the development of inhalable drugs. Its lead product is inhalable insulin, which is in Phase III clinical trials. The company has development agreements with a number of pharmaceutical companies, including:

- Aventis Behring (formerly Centeon) for inhalable α-1 proteinase inhibitor to treat congenital emphysema (phase 1)
- Biogen for inhalable AVONEX (interferon β-1a) (phase 1) to treat multiple sclerosis
- Lilly for an undisclosed inhalable protein (preclinical)
- Pfizer, which is partnered with Aventis Pharma to co-develop and co-promote inhalable insulin

Inhale uses unique proprietary technologies to formulate drugs for dry powder aerosol delivery.

Table 1. Macromolecule Candidates for Pulmonary Delivery

Insulin[15–17]
Alpha$_1$-proteinase inhibitor[18]
Growth hormones[19,20]
Interferons[21,22]
Colony-stimulating factors[23–25]
Erythropoietins
Human calcitonin[22]
Somatostatin analogs
Luteinizing hormone releasing hormone (LHRH) analogs[26]
Factor IX
Vaccines
Interleukins and antagonists
Anti-obesity peptides
Parathyroid hormone[22]
Osteoporosis peptides
Diabetes peptides
Antibodies
Immune suppression peptides
Nerve growth factors

Table 2. Medical Conditions that Could Benefit from Pulmonary Delivery

Pain
Panic and anxiety
Anaphylaxis
Cardiac arrhythmias
Other cardiovascular conditions
Diarrhea
Spasms
Insomnia
Nausea and vomiting
Nicotine withdrawal
Urinary incontinence

The Future of Inhalable Therapeutics

The future of pulmonary drug delivery, whether for macromolecules or small molecules, appears to be broadening. Delivery of macromolecules to the lung periphery offers many advantages over injection and other noninvasive methods. As the fields of biotechnology, genome research, and protein therapeutics continue to burgeon, the opportunities for aerosol delivery of these compounds expand accordingly (Table 1).

Interest is also focused on formulating certain small-molecule pharmaceuticals for pulmonary delivery. Although many of these drugs are readily administered in oral preparations, pulmonary delivery would offer substantial advantages over oral delivery, including rapid onset of the action, in a matter of seconds, and avoidance of the problems that can accompany gastrointestinal absorption, such as low solubility and low bioavailability of the drug, possible gastrointestinal upset caused by drug irritability, unwanted metabolites resulting from gastrointestinal metabolism, and the interaction of the drug and certain foods (Table 2).

Summary

Although oral and injectable drug formulations still dominate the market, interest in pulmonary delivery has been rising steadily. Given patients' desire for an alternative to injections, and recent advances in aerosol science and pulmonary medicine, the potential for improved disease management outcomes by using aerosols for systemic drug delivery should lead the way for a shift to inhalables.

REFERENCES

1. Costa B, Estopa A, Borras J, Sabate A. [Diabetes and pharmacoeconomics: efficiency of insulin injection methods available in Spain]. Aten Primaria 1995;16(7):391–396. (article in Spanish)

2. Illum L, Fischer AN. Intranasal delivery of peptides and proteins. In: Adjei AL, Gupta PK, editors. Inhalation delivery of therapeutic peptides and proteins. New York: Marcel Dekker; 1997: 135–184.
3. Patton JS. Mechanisms of macromolecule absorption by the lungs. Adv Drug Deliv Rev 1996;19:3–36.
4. American Conference of Governmental Industrial Hygienists. Threshold limit values for chemical substances and physical agents and biological exposure indices, 1992–1993. Cincinnati, OH: American Conference of Governmental Industrial Hygienists; 1993: 29.
5. Mackay M, Phillips J, Steward A, Hastewell J. Pulmonary absorption of therapeutic peptides and proteins. In: Byron P, editor. Respiratory Drug Delivery IV conference proceedings. University of Virginia 1994:31–37.
6. Adjeji AL, Gupta PK, editors. Inhalation delivery of therapeutic peptides and proteins. New York: Marcel Dekker; 1997.
7. Niven RW. Delivery of biotherapeutics by inhalation aerosol. Crit Rev Ther Drug Carrier Syst 1995;12(2–3):151–231.
8. Adjei A, Gupta P. Pulmonary delivery of therapeutic peptides and proteins. J Controlled Release 1994;29:361–373.
9. Byron PR, Patton JS. Drug delivery via the respiratory tract. J Aerosol Med 1994 7(1):49–75.
10. Patton JS, Platz RM. Pulmonary delivery of peptides and proteins for systemic action. Adv Drug Deliv Rev 1992;8:179–228.
11. Ward JJ, Hess DR, Helmholz HF Jr. Humidity and aerosol therapy. In: Burton JG, Hodgkin JE, Ward JJ. Respiratory care: a guide to clinical practice, 4th ed. Philadelphia: Lippincott; 1997:421–468.
12. Byron PR. Prediction of drug residence times in regions of the human respiratory tract following aerosol inhalation. J Pharm Sci 1986; 75:433–438.
13. Lalor CB, Hickey AJ. Generation and characterization of aerosols for drug delivery to the lungs. In: Adjei AL, Gupta PK, editors. Inhalation delivery of therapeutic peptides and proteins. New York: Marcel Dekker; 1997: 235–276.
14. O'Riordan TG, Palmer LB, Smaldone GC. Aerosol deposition in mechanically ventilated patients: optimizing nebulizer delivery. Am J Respir Crit Care Med 1994;149(1):214–219.
15. Patton JS, Platz RM. Aerosol insulin: a brief review. In: Byron P, editor. Respiratory Drug Delivery IV conference proceedings. University of Virginia 1994:65–74.
16. Colthorpe P, FarR SJ, Taylor G,. Smith IJ, Wyatt D. The pharmacokinetics of pulmonary-delivered insulin: a comparison of intratracheal and aerosol administration to the rabbit. Pharm Res 1992;9(6): 764–768.
17. Patton J, Bukar J, Nagarajan S. Inhaled insulin. Adv Drug Deliv Rev 1999;35:235–247.
18. Hubbard RC, Brantly ML, Sellers SE, Mitchell ME, Crystal RG. Anti-neutrophil-elastase defenses of the lower respiratory tract in alpha 1-antitrypsin deficiency directly augmented with an aerosol of alpha 1-antitrypsin. Ann Intern Med 1989;111(3):206–212.
19. Patton JS, McCabe JG, Hansen SE, Daugherty AL. Absorption of human growth hormone from the rat lung. Biotechnol Ther 1989–90;1(3):213–228.
20. Colthorpe P, Farr SJ, Sith IJ, Wyatt D, Taylor G. The influence of regional deposition on the pharmacokinetics of pulmonary-delivered human growth hormone in rabbits. Pharm Res 1995;12(3):356–359.
21. Martin RJ, Boguniewicz M, Henson JE, Celniker AC, Williams M, Giorno RC, Leung DYM. The effects of inhaled interferon gamma in normal human airways. Am Rev Respir Dis 1993;148(6 Pt 1):1677–1682.
22. Patton JS, Trinchero P, Platz RM. Bioavailability of pulmonary delivery peptides and proteins: alpha-interferon, calcitonins and parathyroid hormone. J Controlled Release 1994;28:79–85.
23. Niven RW, Whitcomb KL, Shaner L, Ip AY, Kinstler OB. The pulmonary absorption of aerosolized and intratrachealy instilled rhG-CSF and monoPEGylated rhG-CSF. Pharm Res 1995;12(9):1343–1349.
24. Niven RW, Lott, FD, Cribbs JM. Pulmonary absorption of recombinant methionyl human granulocyte colony stimulation factor (r-huG-CSF) after intratracheal instillation to the hamster. Pharm Res 1993;10(11):1604–1610.
25. Niven RW, Lott FD, Ip AY, Cribbs JM. Pulmonary delivery of powders and solutions containing recombinant human granulocyte colony-stimulating factor (rhG-CSF) to the rabbit. Pharm Res 1994; 11(8):1101–1109.
26. Adjei AL, Carrigan PJ. Pulmonary bioavailability of LH-RH analogs: Some biopharmaceutical guidelines. J Biopharm Sci 1992;3(1–2):247–254.

Inhaled Antimicrobial Therapy: From Cystic Fibrosis to the Flu

Thomas G O'Riordan MD

Introduction
Dosing of Inhaled Antimicrobials
Antibacterials: Cystic Fibrosis
  Suppressive Therapy
  Acute Exacerbations
  Eradication/Prevention of Colonization
Antibacterials: Mechanical Ventilation
Pentamidine
Antifungal
Antiviral
  Ribavirin
  Zanamivir
Summary
[Respir Care 2000;45(7):836–845] *Key words: inhaled, antimicrobial, antifungal, antiviral, cystic fibrosis, influenza.*

Introduction

The prospect of delivering antimicrobial therapy directly to the respiratory tract using aerosols has always been attractive to clinicians. Unfortunately, despite 50 years of experience with aerosolizing a wide variety of agents to treat many diseases, there remain relatively few proven indications for this mode of therapy.[1–3] By far the greatest clinical experience with aerosolized antimicrobial therapy is in the treatment of cystic fibrosis. However, even in cystic fibrosis, in which aerosolized antibiotics have had widespread use for several decades, large well controlled studies have only recently established the effectiveness of aerosolized antibiotic therapy.[4,5]

Thomas G O'Riordan MD is affiliated with the Division of Pulmonary and Critical Care Medicine, State University of New York at Stony Brook, Stony Brook, New York.

A version of this paper was presented by Dr O'Riordan during the New Horizons Symposium, "Clinical Pharmacology of Inhaled Agents for the Respiratory Care Clinician," at the American Association for Respiratory Care's 45th International Respiratory Congress, December 14, 1999, in Las Vegas, Nevada.

Correspondence: Thomas G O'Riordan MD, Division of Pulmonary and Critical Care Medicine, SUNY at Stony Brook, Stony Brook NY 11794-8172. E-mail: toriordan@mail.som.sunysb.edu.

The successful development of aerosolized antimicrobial therapy depends on three major factors: the nature of the disease process, the delivery system, and the antimicrobial agent.[6,7] Diseases that involve infection of the airway without a substantial systemic component (eg, cystic fibrosis, bronchiectasis) are much more suitable for aerosolized therapy than diseases of the parenchyma that are associated with substantial risk of systemic complications (eg, pneumococcal pneumonia). The sophistication of aerosol delivery systems has also greatly increased over the past decades. The crude atomizers that produced largely nonrespirable aerosols that were used in the early days of aerosolized antibiotic therapy have given way to modern jet and ultrasonic nebulizers and dry powder devices that produce particles that are much more likely to be respirable and can therefore be targeted to the lower airways.

The third factor is the nature of the antimicrobial agent. Until recently, inhaled antimicrobial therapy consisted of empirical trials of aerosolization of intravenous antibiotic formulations. However, the pharmaceutical industry has in recent years developed specialized formulations of existing agents that are designed for pulmonary delivery (eg, tobramycin[5] and pentamidine[8]). In addition, advances in molecular pharmacology are likely to give rise to a wide variety of new chemical entities that may be suitable for aerosol delivery (eg, zanamivir, which is currently used to treat influenza[9]). With the continued development of new

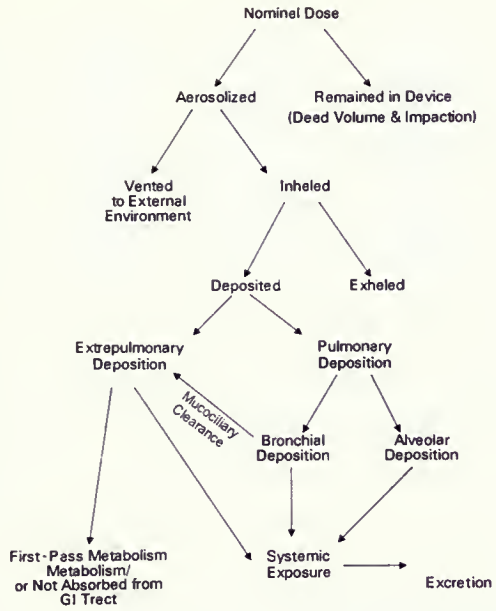


Fig. 1. Schematic outlining the factors that prevent extrapolation of lung dose from the nominal dose placed in the delivery system. (From Reference 7, with permission.)

aerosol delivery systems that can be used to target specific regions of the lung with greater degrees of accuracy, and with the development of new formulations or the discovery of new chemical entities, it is likely that the acceptance of aerosolized drug delivery will continue to grow in the near future.

Dosing of Inhaled Antimicrobials

In contrast to studies of inhaled bronchodilators or bronchoprovocative agents, in which administration of a single dose results in readily quantifiable changes in airway mechanics, detecting the response to inhaled antimicrobial agents often requires multiple doses and tends to be qualitative as well as quantitative. Furthermore, the relationship between nominal dose and bioavailability is much more difficult to characterize than is the case with oral antimicrobial therapy. To further complicate this issue, the regional distribution of the dose (eg, deposition in extrapulmonary regions vs central airways vs alveolar regions) may be as important as the dose depositing in the patient.

Before reviewing individual agents, let us briefly review some of the principles related to dosing of these agents. Figure 1 indicates some of the reasons why we cannot extrapolate the dose delivered to the lung from the nominal dose.[7] The confounding factors can, however, be grouped in ways that may facilitate the development of logical strategies to optimize drug delivery. First, there are factors related to the delivery system, such as differences in output and particle size between different commercial delivery systems, the effects of tubing, holding chambers and other connections, and changes in drug formulation or dilution of solutions and suspensions for nebulization. All of these variables can be assessed in vitro prior to clinical studies. Furthermore, replication of inspiratory breathing patterns of the target population can be readily incorporated into bench models.[10]

However, there is a second group of factors that are much more difficult to replicate in vitro and that usually require clinical studies.[11] These factors determine the fate of a particle after it is inhaled. Once an aerosolized drug particle of a given size has been inhaled at a given flow, the site of deposition is influenced by the anatomy of the upper and lower airways and by the patient's breathing pattern, including breath-holding and the presence of expiratory flow limitation.[6] Furthermore, the aerodynamic characteristics of an aqueous aerosol may be altered by the relative humidity of the airway.[12]

Measuring the dose delivered to the lung is the most difficult part of the dosimetry outlined in Figure 1, and has been reviewed elsewhere.[6,7] Gamma scintigraphy is a technique by which the deposition of a radiotracer mixed with the drug being studied is measured using a gamma camera.[6,13,14] It can be used to measure the total dose delivered to the lung, and to assess the regional distribution of deposited radioactivity (eg, extrapulmonary versus pulmonary, or central airways versus lung periphery).

To quantify the dose delivered to the patient without measuring the regional distribution, there are a number of alternatives to gamma scintigraphy. For example, filters or laser diffraction devices, placed near the patient's mouth, can measure the drug delivered during inhalation and exhalation, and drug deposition is equal to the difference between the amounts inhaled and exhaled.[14] If the aerosol does not contain a substantial fraction of particles $> 5\ \mu m$ in diameter, such measurements are an accurate reflection of pulmonary drug deposition because relatively little drug will deposit in the pharynx during tidal breathing.

Pharmacokinetic assessments, sometimes combined with gamma techniques, are useful in characterizing the pulmonary deposition of inhaled antimicrobials.[15–17] For example, Ilowite et al reported that sputum levels of gentamicin were two orders of magnitude greater than levels expected using the systemic route.[15] However, sputum concentrations were more reflective of deposition in the central airways than of the total amount of drug deposited in the lung.

In addition to measuring drug levels in serum and respiratory secretions, urine collection for drug concentrations is a useful measure of the systemic bioavailability of inhaled aminoglycosides[15] and pentamidine.[16] Systemic bioavailability is useful as an indicator of the adequacy of

pulmonary drug delivery and as a safety index of the degree of exposure of other organ systems to the drug.

Antibacterials: Cystic Fibrosis

In a majority of patients with cystic fibrosis and bronchiectasis, the airways are usually colonized by Gram-negative organisms such as *Pseudomonas aeruginosa*. After persistent colonization, the *P. aeruginosa* is usually of mucoid phenotype associated with reduced penetration of antibiotics in airway secretions. Aminoglycosides, because of their poor penetration into sputum following intravenous administration,[18] their potential for toxicity with high doses and prolonged concentration, and their activity against *P. aeruginosa* have been the most frequently prescribed inhaled antibiotics in cystic fibrosis.[19,20] Tobramycin is the most frequently used aerosolized antibiotic because of higher rates of resistance with gentamicin and the higher cost of amikacin. Other antibiotics administered via inhalation include colistin[1,2,21,22] and a few reports of cephalosporins.[23] With the exception of the quinolones, these organisms are not usually sensitive to oral antibiotics and require intravenous antibiotic therapy. Unfortunately, after the colonization process has been established, intravenous antibiotic therapy is usually suppressive rather than eradicative.

Repeated courses of intravenous antibiotics lead to the development of drug resistance, as well to the complications associated with obtaining venous access for a long period of time. Though such suppressive therapy with aerosolized antibiotics has been undertaken for many years, large multicenter studies have only recently established that this treatment is in fact safe and effective. In a new formulation of tobramycin (TOBI, tobramycin solution for inhalation, PathoGenesis, Seattle), it has been found that administration of this agent twice a day for 28 days on alternate months is associated with improved pulmonary function and reduced rates of acute exacerbation. However, though suppressive therapy is the most common indication for prescribing aerosolized antibiotics in cystic fibrosis, there are two other areas of interest for the use of aerosolized antibiotics in cystic fibrosis. One is the use of aerosolized antibiotics to eradicate Gram-negative organisms in early disease and prevent colonization. The other is their potential as an adjunct to intravenous therapy in acute exacerbations.

Overall, the results of earlier inhaled antibiotic studies were somewhat difficult to interpret because of differences in study design. The doses of antibiotics have differed between studies and some may not have been adequately blinded because of the distinctive taste of some aerosolized agents. Likewise, the delivered dose has varied because of the use of different nebulizers and drug formulations.

Suppressive Therapy

Most of the clinical trials of inhaled antibiotics have concentrated on suppressive therapy in the period between acute exacerbations. The findings of these studies have been reviewed in greater detail elsewhere.[1–3,18–22] Conclusions are difficult to draw from integration of these studies because of differences in study design, dosage, and delivery system. The majority of aminoglycoside studies used aerosolized tobramycin compounded from intravenous formulations. However, though earlier studies used lower doses and yielded various results, two recent large multicenter trials provided convincing evidence of the efficacy of aerosolized tobramycin therapy in cystic fibrosis.[4,5] In the first of these studies,[4] 71 patients were randomized to one of two groups. Group 1 received 600 mg of aerosolized tobramycin for 28 days, followed by placebo for two 28-day periods. Group 2 received placebo for 28 days, followed by tobramycin for two 28-day periods. Pulmonary function and the density of *P. aeruginosa* in sputum were assessed. Treatment with tobramycin in the first 28-day period was associated with a significant increase in forced expiratory volume in the first second (FEV_1) percent of predicted ($p < 0.0001$) and forced vital capacity, compared to placebo. A decrease in the density of *P. aeruginosa* in sputum, by a factor of 100, was found during all periods of tobramycin administration. Analysis of the three-period crossover demonstrated that tobramycin administration was associated with improvement in FEV_1 but that the magnitude of the treatment effect was approximately half the magnitude observed in the first period parallel analysis. No significant difference was found between tobramycin and placebo for forced vital capacity. No ototoxicity or nephrotoxicity occurred, and the emergence of tobramycin-resistant bacteria was similar between the treatment groups. Lastly, a treatment effect was maintained during a 28-day off-drug period after an initial 28-day on-drug period (600 mg tobramycin tid), suggesting that continuous therapy was not required to maintain improvements in pulmonary function.

Most recently, in a multicenter, controlled study, Ramsey et al[5] assessed TOBI, a formulation of tobramycin specifically designed for aerosolization. TOBI is a sterile, preservative-free solution containing 60 mg/mL of tobramycin. It is to be used in conjunction with the PARI-LC Plus jet nebulizer with a DeVilbiss Pulmo-Aide compressor. Two pivotal studies using TOBI at a dose of 300 mg bid demonstrated its safety and efficacy in cystic fibrosis patients. Because the aerosol was better characterized and the delivery system was probably more efficient, these utilized a lower dose and twice-daily administration, compared to the earlier 1993 study by Ramsey et al.[4] A total of 520 patients were randomly assigned to receive either 300 mg of inhaled tobramycin or placebo twice daily for 4

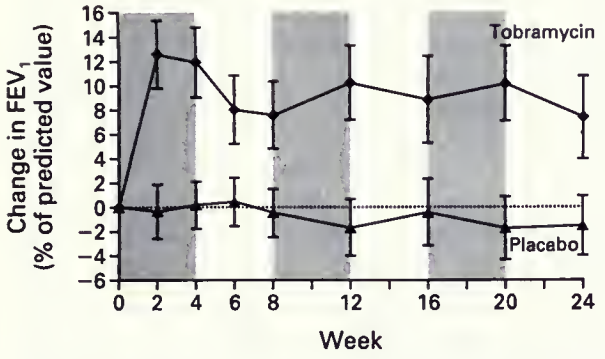


Fig. 2. Mean change in forced expiratory volume in the first second (FEV_1) percent of predicted (± 95% confidence interval) over 24 weeks in subjects receiving either tobramycin or placebo. The "on drug" boxes (shaded areas) denote periods when subjects were on either inhaled tobramycin solution (TOBI) or placebo. (From Reference 5, with permission.)

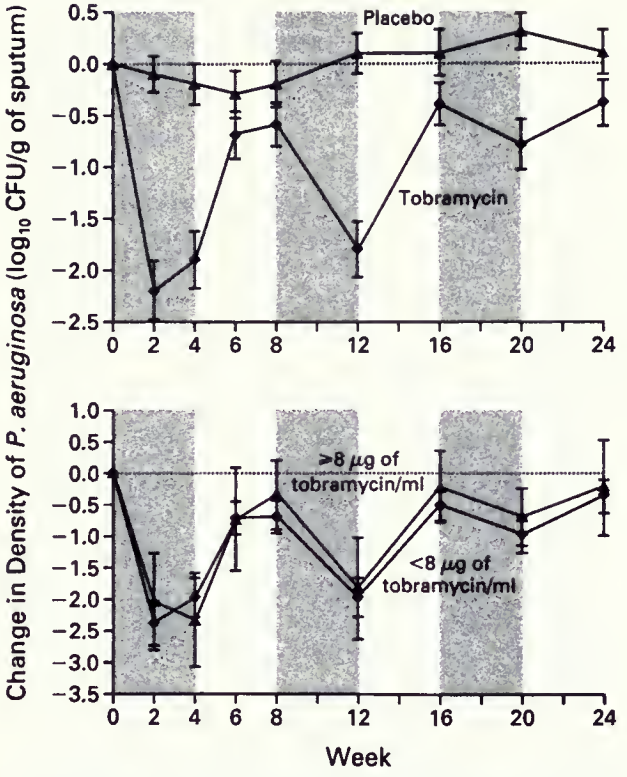


Fig. 3. Mean change in sputum *P. aeruginosa* density (± 95% CI) over 24 weeks in subjects receiving either tobramycin or placebo. The "on drug" boxes (shaded areas) denote periods when subjects were on either inhaled tobramycin solution (TOBI) or placebo. (From Reference 5, with permission.)

weeks, followed by 4 weeks with no study drug. Treatment or placebo in 3 on-off cycles was administered for a total of 24 weeks. The end points included pulmonary function, the density of *P. aeruginosa* in sputum, and hospitalization. Patients treated with tobramycin had an average FEV_1 increase of 10% at week 20, as compared with week 0, whereas the patients receiving placebo had a 2% FEV_1 decrease (Fig. 2). During each period when the drug was not being administered, improvement in lung function was maintained while the density of *P. aeruginosa* sputum returned toward baseline values (Fig. 3). Treatment with tobramycin decreased the density of *P. aeruginosa* sputum and also decreased the risk of hospitalization. Subgroup analysis revealed that the most impressive response to TOBI was in teenagers, an important finding, because this group tends to have the most rapid rate of decline in lung function (Table 1). Tinnitus and alteration of the voice were the only adverse events reported in a significantly greater percentage of the tobramycin group than in the placebo group. The 8 cases of tinnitus reported in the tobramycin group were transient and mild or moderate in severity and did not lead to withdrawal from the study. Likewise, voice alteration was mild in most cases. No nephrotoxicity was detected. TOBI has superseded the "off label" use of parenteral formulations of tobramycin that contain preservatives and the safety of which for delivery via inhalation has not been adequately assessed.

Polymyxins are cyclic polypeptide antibiotics. Over several decades, at least three polymyxin preparations (polymyxin B sulphate, colistin sulphate, and colistin sulphomethate sodium) have been administered via aerosol to cystic fibrosis patients.[2,21,22] At present in the United States, only colistin sulphomethate (Coly-Mycin) is approved for parenteral use, and it has less systemic toxicity than the other two agents. Coly-Mycin has high activity against *P. aeruginosa*, but *Burkholderia cepacia* is often resistant. However, the "off label" use of parenteral Coly-Mycin for aerosol therapy is not supported by adequate and well controlled trials demonstrating its efficacy and safety, and it is associated (as are other polymyxins) with a substantial risk of severe bronchospasm, even after pretreatment with a β-2 adrenergic agonist.

Acute Exacerbations

In the treatment of acute respiratory exacerbations in cystic fibrosis patients, studies suggest that the addition of aerosolized antibiotics to intravenous antibiotic therapy offers little additional benefit.[24,25] No significant improvement in symptoms, pulmonary function, or prevention of recolonization was noted when inhaled aminoglycosides were administered in conjunction with intravenous aminoglycosides and antipseudomonal β lactams.[24] Although this adjunctive inhaled aminoglycoside therapy led to increased rates of eradication of *P. aeruginosa*, compared to intravenous therapy alone, the eradication was transient and there was no correlation between bacteriologic response and clinical improvement.[24] However, because these small studies may indicate a trend in favor of increased rates of

Table 1. Response to Inhaled Tobramycin Subanalysis by Age of Subjects

Subgroup	No. of Patients	Mean Change in FEV_1		Treatment Effect*	p Value†
		Tobramycin	Placebo		
Age					0.005
6–12 y	113	14.11	5.52	8.59	0.08
13–17 y	120	15.88	−7.15	23.03	< 0.001
≥18 y	229	5.52	−2.64	8.16	< 0.001
Sex					0.12
Male	246	8.67	−0.30	8.97	< 0.001
Female	216	11.96	−3.24	15.20	< 0.001
Disease severity					0.88
FEV_1 < 50% of predicted	209	8.38	−3.83	12.21	< 0.001
FEV_1 ≥ 50% of predicted	253	11.50	−0.12	11.62	< 0.001
Use of dornase alfa					0.2
Yes	320	11.28	−2.28	13.56	< 0.001
No	142	7.38	−0.68	8.06	0.02
All patients	462	10.08	−1.79	11.87	< 0.001

FEV_1 = forced expiratory volume in the first second.
*The treatment effect was calculated as the difference between the mean changes in the tobramycin and placebo groups.
†For each subgroup, the first p value is for the overall comparison of the two treatment groups by analysis of variance; the other p values are for subgroup-treatment interactions.
The largest response in FEV_1 was in teenage subjects, the smallest in adults.
(Adapted from Reference 5, with permission.)

eradication with adjuvant therapy, it may be worth reevaluating this issue with emphasis on either enhanced pulmonary delivery of aerosolized antibiotics or, alternatively, by focusing on subgroups of patients (eg, those with early disease or those with more rapid declines in pulmonary function).

Eradication/Prevention of Colonization

Most studies of aerosolized antibiotics in cystic fibrosis have concentrated on treating or suppressing established infection/colonization, but Valerius et al[22] assessed whether chronic pulmonary colonization with *P. aeruginosa* in cystic fibrosis is preventable. Twenty-six patients who had never received anti-pseudomonal chemotherapy were randomized to receive either no antipseudomonal chemotherapy or oral ciprofloxacin and aerosol inhalations of colistin twice daily for 3 weeks, whenever *P. aeruginosa* was isolated from routine sputum cultures. During the 27 months of the trial, infection with *P. aeruginosa* became chronic in significantly fewer treated subjects than untreated subjects (2 [14%] vs 7 [58%], $p < 0.05$) and there were significantly fewer *P. aeruginosa* isolates in routine sputum cultures in the treated group (49/214 [23%] vs 64/158 [41%], $p = 0.0006$). The authors concluded that chronic colonization with *P. aeruginosa* can be prevented in cystic fibrosis by early institution of antipseudomonal chemotherapy. Though these preliminary data from Denmark are encouraging, this approach requires early detection of the disease, with close follow-up and intensive therapy for patients who are in many cases relatively asymptomatic. In addition, concerns about the emergence of drug resistance with early therapy need to be allayed. However, if these studies can be replicated on a wider scale, delaying the progression to severe disease may justify the expense of early intensive therapy.

Antibacterials: Mechanical Ventilation

Patients undergoing mechanical ventilation are predisposed to develop pneumonia. In addition, if mechanical ventilation is prolonged, a purulent bronchitis can develop that may interfere with attempts to wean the patient from the ventilator and necessitate a tracheostomy. Though the lower airway is sterile in normal subjects, patients undergoing mechanical ventilation quickly become colonized with Gram-negative organisms or *Staplococcus aureus*. Antibiotic resistance is common. Though aerosolized antibiotics have been used for the prophylaxis of pneumonia and for the treatment of bronchitis, neither indication is adequately supported by well controlled trials. However, though the evidence suggests that routine prophylaxis of intubated patients with aerosolized antibiotics may not only be ineffective but could be counterproductive and dangerous,[26] there is preliminary data that aerosolized antibiotics used selectively may have a role in the treatment of purulent tracheobronchitis and may be worthy of further study. In a small open-label feasibility study, administration of nebulized gentamicin to patients undergoing prolonged mechanical ventilation reduced the volume of purulent secre-

tions.[27] However, simply reducing the volume of secretions may not necessarily be clinically important, and a number of key questions await further answers: Does the treatment of purulent tracheobronchitis affect, either beneficially or adversely, the incidence or the course of subsequent ventilator-associated pneumonia? Does such therapy facilitate weaning from mechanical ventilation or decannulation of tracheostomies? Does aerosolized antibiotic therapy promote drug resistance at rates greater than or less than systemic administration?

In order to address any of these issues in a clinically meaningful manner, it will be necessary to establish the dose of drug delivered to the lungs of intubated mechanically ventilated patients. Recent studies demonstrate that it is possible to achieve aminoglycoside levels in the secretions of such patients that are 10–50 times higher than serum concentrations achieved using the same nominal dose administered intravenously.[27] However, in order to achieve such antibiotic concentrations, it is necessary to optimize a number of factors, including the ventilator settings, volume fill of the nebulizer, treatment time, interruption of humidification, and the type of nebulizer and ventilator.[28]

Once it has been established that the drug has been delivered in adequate concentrations, the clinical issues listed in the preceding paragraph can then be explored. In the meantime we can only speculate. We believe that prophylactic or indiscriminate use of an antibiotic by any route, including inhalation, will inevitably lead to antibiotic resistance. However, studies in cystic fibrosis patients suggest that the risk of drug resistance is probably not greater through inhalation than through systemic administration. Furthermore, the high concentrations of drug in secretions achieved with optimized delivery should, theoretically, retard the development of resistance.

Reducing the volume of purulent secretions with antibiotic therapy could facilitate weaning or decannulation in some patients. However, depending on the chronicity of the hypersecretion, in many patients the reduction in volume is likely to be temporary. Though the indiscriminate prophylactic use of inhaled antibiotics is unlikely to be useful, it is not possible at this stage to predict whether intensive therapy of tracheobronchitis will prevent ventilator-associated pneumonia. Controlled clinical trials of aerosolized antibiotics in mechanical ventilation are needed before this mode of therapy can be recommended as effective or safe.

Pentamidine

Aerosolized pentamidine is used as prophylactic therapy against *Pneumocystis carinii* pneumonia (PCP) in patients with human immunodeficiency virus. Prior to its use as an inhaled formulation for PCP prophylaxis, pentamidine had been used for many years as a systemic therapy for tropical protozoal infections and for the treatment of rare cases of PCP in immunocompromised patients. With the advent of the acquired immunodeficiency syndrome/PCP pandemic in the 1980s, the use of intravenous pentamidine greatly increased. Because of the high incidence of PCP in patients with human immunodeficiency virus and the frequency of recurrence of the condition in patients with a prior episode, clinical trials of prophylaxis were undertaken with a formulation designed for inhalation.[8] These studies found that aerosolized pentamidine was effective as secondary prophylaxis in patients with at least one prior episode of PCP and as primary prophylactic therapy in patients with CD4 counts of $< 200/mm^3$. The widespread introduction of aerosolized pentamidine was associated with a significant reduction in the morbidity and mortality associated with PCP. Some reports also suggested that it could be used as therapy for a subset of patients with established PCP,[29] but the inhaled drug is now rarely used for that indication. Even though it has been demonstrated that prophylaxis with trimethoprim-sulfamethoxazole was more effective and less expensive[30] than aerosolized pentamidine, it continues to be used in a subset of patients who are allergic to or intolerant of sulphonamide-containing agents. The cumulative failure rate for aerosolized pentamidine prophylaxis in patients with CD4 counts of $100–200/mm^3$ was reported to be 21% over a 3-year period: a rate comparable to that of trimethoprim-sulfamethoxazole or dapsone.[30] However, in patients with CD4 counts $< 100/mm^3$, the failure rate with aerosolized pentamidine is 33%— significantly higher than with oral regimens. The oral regimens have the added advantages of providing protection against toxoplasmosis and of being less expensive. However, the patients who are more likely to require aerosolized pentamidine treatment because of intolerance to aerosolized pentamidine are also those with CD4 counts $< 100\ mm^3$, and, as a result, aerosolized pentamidine is more likely to be used in the group in whom it is less effective.

Radiologically, PCP usually presents as a diffuse multilobe pneumonia. However, it has been suggested that presentation with upper lobe disease may be more common in patients receiving aerosolized pentamidine.[31] The possible interaction of regional distribution of inhaled pentamidine with the regional distribution of PCP has been discussed elsewhere.[7]

Nebulizers for aerosolized pentamidine therapy have two requirements not routinely fulfilled by commercial jet nebulizers. First, they need to provide small particles (mass median aerodynamic diameter of approximately 1 μm) to optimize delivery to the lung periphery rather than to the central airways. Second, they must incorporate an exhalation filter to reduce environmental contamination. In the United States, the approved nebulizer for aerosolized pen-

tamidine therapy is the Respirgard II (Marquest Medical, Englewood, Colorado), although alternative devices have been used successfully in other countries. Its design incorporates an external baffle to remove large particles from the aerosol, and the treatment time is 40 minutes to nebulize 6 mL, with approximately 10% of the drug depositing in the lung.

Because alveolar clearance of relatively insoluble particles is slow compared to the clearance of particles depositing in ciliated airways (weeks instead of hours), the drug needs to be administered at only 2-week or 4-week intervals. Plasma levels are usually undetectable, but pentamidine is detectable in urine for weeks after administration of a single dose. Urine levels correlate with bronchoalveolar lavage fluid levels.[16]

Aerosolized pentamidine is a relatively safe and well tolerated medication for most patients. The most common adverse effects are cough and bronchospasm. However, pretreatment with a short-acting β-2 agonist can prevent or ameliorate these symptoms in most patients. There is some evidence that the incidence of pneumothorax may be higher in patients taking aerosolized pentamidine.[31] Infection with *Pneumocystis carinii* can result in cystic changes in the lung, which can predispose to pneumothorax formation. Furthermore, if aerosolized pentamidine therapy induces frequent severe bouts of coughing, the risk of pneumothorax would theoretically increase. As a result, the drug should be prescribed with caution in patients considered to be at increased risk of this complication.

A further consideration with the use of aerosolized pentamidine concerns the exposure of health care workers to the drug.[32] Indeed, some health care workers have had urinary levels that approached those of patients. Though most health care workers exposed to aerosolized pentamidine are asymptomatic, there are anecdotal reports of cough, aggravation of asthma, and at least one case of a worker developing a reduction in carbon monoxide diffusing capacity. The risk of exposure is increased by the fact that submicronic particles can stay suspended in room air for several hours and are thus respirable by bystanders. Loose-fitting face masks offer little protection because the inhaled airstream can bypass the mask. However, if patients are treated in well ventilated rooms with negative pressure and adequate air exchange (or, in some centers, specially designed booths), large numbers of patients can be treated without detectable systemic exposure of health care workers.[33] Because the nebulizers that are used for aerosolized pentamidine include exhalation filters, the most important source of health care worker contamination may be inadequately supervised patients removing the device from their mouths either to cough or to converse without first switching off the compressed air supply.[32] Ideally, patients should be observed through a window during treatment, in an adequately ventilated room or booth.

In conclusion, aerosolized pentamidine therapy continues to have a role for the prophylaxis of PCP in patients who are allergic to or otherwise intolerant of oral prophylaxis. The development of aerosolized pentamidine has yielded valuable insights into the evaluation of the dose response of inhaled drugs and increased our awareness of the need to protect health care workers from exposure to inhaled drugs.

Antifungal

Invasive pulmonary aspergillosis is one of the most devastating complications of bone marrow transplantation and aggressive anticancer chemotherapy regimens. Though intravenous amphotericin B is the most effective available treatment, this disease is frequently fulminant and fatal. In efforts to reduce the incidence of this condition, some investigators have prophylactically administered amphotericin B via inhalation. An aqueous formulation and a liposomal formulation have been tested.[34,35] Both are well tolerated but it has not been determined whether one formulation is superior to the other. Theoretically, the liposomal formulation would have a longer residence time in the airway. Pilot studies suggest that inhaled amphotericin B is relatively well tolerated, though cough and wheeze is induced in some patients, especially those with a history of asthma or airway hyperreactivity. It appears that systemic exposure is low after administration via inhalation. Unfortunately, because of insufficient data, it is not possible to determine whether such treatment is effective. No large-scale studies have been published to date. Most studies have examined amphotericin B as prophylaxis for pulmonary aspergillosis in neutropenic patients following bone marrow transplantation, but the results were ambiguous because of inadequate study size or design.[35–39] Because the incidence of this complication is relatively episodic, studies based on historical controls or on small sample sizes are likely to be inconclusive. One study examined the use of aerosolized amphotericin as prophylaxis against fungal infections following lung, heart-lung, and heart transplantation, and found a significant reduction in the incidence of fungal infections, compared to a case control group.[38] At the present time, the role, if any, of inhaled antifungal therapy with amphotericin B remains undetermined. It is regrettable, given the seriousness of pulmonary aspergillosis in immunosuppressed patients, that inhaled amphotericin B, a potentially beneficial prophylactic therapy, has not yet been adequately evaluated.

Antiviral

Ribavirin

Ribavirin therapy for respiratory syncytial virus (RSV) infection was for many years the only accepted inhalation

Table 2. Response to Treatment with Zanamivir or Placebo*

Symptoms	Placebo	Zanamivir	Difference (95% CI)	p	Relative Risk (95% CI)
Complications					
Intention to treat	64/228 (28%)	49/227 (22%)	6% (−2 to 15)	0.135	0.77 (0.56–1.06)
High risk	18/39 (46%)	5/37 (14%)	32% (11 to 54)	0.004	0.29 (0.13–0.64)
Associated antibiotic use					
Intention to treat	52/228 (23%)	45/227 (20%)	3% (−5 to 11)	0.508	0.87 (0.61–1.24)
High risk	15/39 (38%)	5/37 (14%)	25% (3 to 46)	0.025	0.35 (0.15–0.81)

CI = confidence interval.
*Response assessed by development of complications or the need for antibiotic therapy; comparison of high risk patients versus intention to treat.
(Adapted from Reference 9, with permission.)

therapy for viral illness.[39,40] RSV infection is the one of the main causes of acute bronchiolitis in children, most of whom are less than three years old.[40] Inhaled drug delivery in very young patients poses technical challenges, and the drug is delivered via humidification tents or face masks. It has also been delivered to patients undergoing mechanical ventilation. However, in the latter setting considerable caution is required because the drug can precipitate in and obstruct ventilator tubing. The drug is delivered by way of a specialized small-particle aerosol generator supplied with the drug. This is the only device that should be used to deliver the drug, and ribavirin should not be mixed with other agents.[39] Though the small-particle aerosol generator can be incorporated, with suitable precautions and adjustments, into mechanical ventilator circuits, it is recommended that such therapy be administered in centers with prior experience in this relatively complex protocol. Despite the extensive clinical experience with this drug, some controversy continues about its efficacy. It appears effective at reducing viral shedding from respiratory mucosa in patients with RSV, and most studies agree that if it is administered early in the course of illness, the duration and severity are shortened. In mechanical ventilation, controversy persists. One study that reported considerable benefit was subsequently criticized for having used water as a control.[41] A later study, which used a saline control, reported a lack of efficacy, but was in turn criticized as underpowered.[42] The current American Academy of Pediatrics recommendation is that this agent be considered in the setting of respiratory failure due to RSV and that requires mechanical ventilation. In addition to RSV, aerosolized ribavirin may have activity against influenza[43] and adenovirus infections. When delivered parentally it has been reported as being useful in treating Hanta virus infection and Lassa fever.[39]

Ribavirin is well tolerated but can precipitate cough and bronchospasm in occasional subjects. Though at least 20 deaths have been reported as possibly due to ribavirin administration, the severity of the patients' conditions makes a causal relationship difficult to establish.[39,40] Though human teratogenicity is unproven, there is persuasive evidence that ribavirin is teratogenic in most species studied. Thus, the drug should not be administered to women who may become pregnant or to lactating mothers. In addition, concern has been expressed about the potential dangers to health care workers exposed to ambient drug, and it is important that efforts be made to minimize exposure.[38]

Zanamivir

Zanamivir is a new antiviral agent that is specific for influenza A and B. The mechanism of action of zanamivir is inhibition of neuraminidase, an enzyme that is important for releasing newly formed influenza viral particles from the surface of the infected cell. Inhibition of this enzyme effectively disrupts viral replication. The drug is well tolerated, with a pattern of adverse effects similar to that of placebo. Zanamivir is delivered as a powder from a multi-

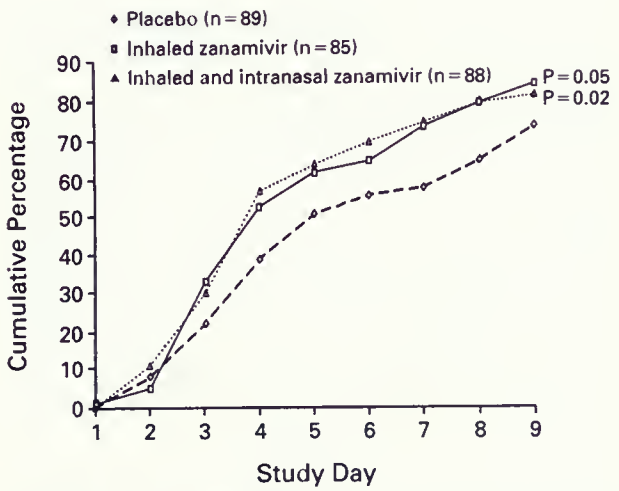


Fig. 4. Response to treatment with zanamivir (inhaled), zanamivir (inhaled plus intranasal), or placebo, as assessed by the persistence of symptoms. (From Reference 45, with permission.)

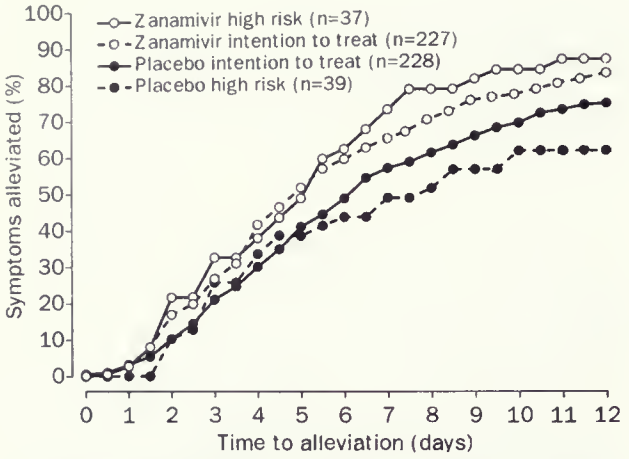

Zanamivir high risk (n=37)
Zanamivir intention to treat (n=227)
Placebo intention to treat (n=228)
Placebo high risk (n=39)
Symptoms alleviated (%)
Time to alleviation (days)

Fig. 5. Response to treatment with zanamivir or placebo as assessed by the persistence of symptoms; comparison of high-risk patients versus intention to treat. (From Reference 9, with permission.)

dose inhaler called the Diskhaler. The drug has low oral bioavailability and is renally excreted.

Influenza affects about a hundred million Americans in a given year and is associated with about 40,000 deaths per year.[44] There are generally three courses for influenza infection:

1. An uncomplicated illness of approximately one week's duration. This usually occurs in previously healthy patients, and it is in this group that zanamivir has been extensively tested. Studies demonstrate that the use of zanamivir can significantly shorten the duration of influenza symptoms (Fig. 4).[9,45] Studies of its possible prophylactic role in subjects at risk of contracting the illness (eg, household contacts of patients with influenza) are in progress.

2. Influenza infection may progress rapidly to viral pneumonia. There are no data on the role of Zanamivir in this group.

3. After an initial improvement the patient deteriorates, with evidence of a secondary bacterial pneumonia or purulent tracheobronchitis. Many of these patients have preexisting chronic respiratory disease. The drug has not been widely tested in asthma or bronchitis patients. Because of some reports of cough and bronchospasm, the drug should be used with caution in such patients. It should be emphasized that if patients with clinical evidence of bacterial superinfection are given zanamivir, that they should also receive broad spectrum antibiotic therapy. Though there is some preliminary data that zanamivir therapy may reduce the likelihood of needing antibiotic therapy in patients that are immunocompromised because of a pre-existing respiratory disease[11] (see Table 2 and Fig. 5),[45] these data are limited, and additional studies are needed in compromised patients.

Summary

Recent controlled clinical trials have confirmed the usefulness of aerosolized tobramycin in cystic fibrosis and have emphasized the importance of ensuring adequate lung delivery of inhaled antimicrobials. For purulent tracheobronchitis associated with prolonged mechanical ventilation it has recently been established that it is possible to deliver substantial and measurable doses of medications to the airway via aerosolization, but controlled studies are needed to determine the efficacy and safety of inhaled antibiotic therapy in this setting. However, prophylactic aerosolized antibiotic therapy in an intensive care unit setting may be counterproductive. Aerosolized pentamidine continues to provide prophylaxis against PCP in a substantial minority of subjects with human immunodeficiency virus infection who are intolerant of oral agents. The effectiveness of aerosolized amphotericin B as prophylaxis against aspergillosis in neutropenic patients needs to be evaluated in a large clinical trial. Zanamivir, an inhibitor of neuraminidase, delivered via inhalation, shows promise in the treatment of uncomplicated influenza infection, but more data are needed on its effectiveness and safety in patients with preexisting respiratory disease. The development of new chemical entities, more efficient delivery systems, and more precise measurement of dose-response and regional pulmonary drug distribution of inhaled antimicrobials suggest that this somewhat neglected topic in therapeutics may be about to receive an increased degree of attention.

REFERENCES

1. Toso C, Williams DM, Noone PG. Inhaled antibiotics in cystic fibrosis: a review. Ann Pharmacother 1996;30(7-8):840–850.
2. Pines A, Raafat H, Plucinski K. Gentamicin and colistin in chronic purulent bronchial infections. Br Med J 1967;2(551):543–545.
3. Bryson V, Sansome E, Laskin S. Aerosolization of penicillin solutions. Science 1944;100:33–35.
4. Ramsey BW, Dorkin HL, Eisenberg JD, Gibson RL, Harwood IR, Kravitz RM, et al. Efficacy of aerosolized tobramycin in patients with cystic fibrosis. N Engl J Med 1993;328(24):1740–1746.
5. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med 1999;340(1):23–30.
6. Smaldone GC, O'Riordan TG. Aerosol deposition and clearance. In: Wagner HN, editor. Principles of nuclear medicine, 2nd ed. Philadelphia: WB Saunders; 1995: 895–905.
7. O'Riordan TG, Faris M. Inhaled antimicrobial therapy. Respir Care Clin N Am 1999;5(4):617–631.
8. Leoung GS, Feigal DW Jr., Montgomery AB, Corkery K, Wardlaw L, Adams M, et al. Aerosolized pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia: the San Francisco community prophylaxis trial. New Engl J Med 1990;323(12):769–775.
9. Randomised trial of efficacy and safety of inhaled zanamivir in treatment of influenza A and B virus infections. The MIST (Management of Influenza in the Southern Hemisphere Trialists) Study Group. Lancet 1998;352(9144):1877–1881.
10. Smaldone GC. Drug delivery via aerosol systems: concept of "aerosol inhaled". J Aerosol Med 1991;4(3):229–235.

11. Bennett WD. Aerosolized drug delivery: fractional deposition of inhaled particles. J Aerosol Med 1991;4(13):223–229.
12. Hiller FC. Health implications of hygroscopic particle growth in the human respiratory tract. J Aerosol Med 1991;4:1–23.
13. Davis SS, Hardy JG, Newman SP, Wilding IR. Gamma scintigraphy in the evaluation of pharmaceutical dosage forms (review). Eur J Nucl Med 1992;19(11):971–986.
14. Smaldone GC, Fuhrer J, Steigbigel RT, McPeck M. Factors determining pulmonary deposition of aerosolized pentamidine in patients with human immunodeficiency virus infection. Am Rev Respir Dis 1991;143(4 Pt 1):727–737.
15. Howite JS, Gorvoy JD, Smaldone GC. Quantitative deposition of aerosolized gentamicin in cystic fibrosis. Am Rev Respir Dis 1987; 136(6):1445–1449.
16. Smaldone GC, Vinciguerra C, Morra L. Urine pentamidine as an indicator of lung pentamidine in patients receiving aerosol therapy. Chest 1991;100(5):1219–1223.
17. Le Conte P, Potel G, Peltier P, Horeau D, Caillon J, Juvin ME, et al. Lung distribution and pharmacokinetics of aerosolized tobramycin. Am Rev Respir Dis 1993;147(5):1279–1282.
18. Mendelman PM, Smith AL, Levy J, Weber A, Ramsey B, Davis RL. Aminoglycoside penetration, inactivation, and efficacy in cystic fibrosis sputum. Am Rev Respir Dis 1985;132(4):761–765.
19. Hodson ME, Penketh ARL, Batten JC. Aerosol carbenicillin and gentamicin treatment of *Pseudomonas aeruginosa* infection in patients with cystic fibrosis. Lancet 1981;2(8256):1137–1139.
20. MacLusky IB, Gold R, Corey M, Levison H. Long-term effects of inhaled tobramycin in patients with cystic fibrosis colonized with *Pseudomonas aeruginosa*. Pediatr Pulmonol 1989;7(1):42–48.
21. Jensen T, Pedersen SS, Garne S, Heilmann C, Hoiby N, Koch C. Colistin inhalation therapy in cystic fibrosis patients with chronic *Pseudomonas aeruginosa* lung infection. J Antimicrob Chemother 1987;19:831–838.
22. Valerius NH, Koch C, Hoiby N. Prevention of chronic *Pseudomonas aeruginosa* colonisation in cystic fibrosis by early treatment. Lancet 1991;338(8769):725–726.
23. Nolan G, Moivor P, Levison H, Fleming PC, Corey M, Gold R. Antibiotics prophylaxis in cystic fibrosis: inhaled cephaloradine as an adjunct to oral cloxacillin. J Pediatr 1982;101(4):626–630.
24. Schaad UB, Wedgewood, Krucko J, Suter S, Kraemer R. Efficacy of inhaled amikacin as adjunct to intravenous combination therapy (ceftazidime and amikacin) in cystic fibrosis. J Pediatr 1987;111(4):599–605.
25. Stephens D, Garey N, Isles A, Levison H, Gold R. Efficacy of inhaled tobramycin in the treatment of pulmonary exacerbations in children with cystic fibrosis. Pediatr Infect Dis 1983;2(3):209–211.
26. Feeley TW, Du Moulin GC, Hedley-Whyte J, Bushnell LS, Gilbert JP, Feingold DS. Aerosol polymyxin and pneumonia in seriously ill patients. New Engl J Med 1975;293(10):471–475.
27. Palmer LB, Smaldone GC, Simon SR, O'Riordan TG, Cuccia A. Aerosolized antibiotics in mechanically ventilated patients: delivery and response. Crit Care Med 1999;26(1):31–39.
28. O'Riordan TG, Palmer LB, Smaldone GC. Aerosol deposition in mechanically ventilated patients: optimizing nebulizer delivery. Am J Respir Crit Care Med 1994;149(1):214–219.
29. Montgomery AB, Debs RJ, Luce JM, Corkery KJ, Turner J, Brunette EN, Lin ET, Hopewell PC. Aerosolised pentamidine as sole therapy for *Pneumocystis carinii* pneumonia in patients with acquired immunodeficiency syndrome. Lancet 1987;2(8557):480–483.
30. Bozzette SA, Finkelstein DM, Spector SA, Frame P, Powderly WG, He W, et al. A randomized trial of three antipneumocystis agents in patients with advanced human immunodeficiency virus infection. NIAID AIDS Clinical Trials. New Engl J Med 1995:332(11):693–699.
31. Jules-Elysee K, Stover DE, Zaman MB, Bernard EM, White DA. Aerosolized pentamidine: effect on diagnosis and presentation of *Pneumocystis carinii* pneumonia. Ann Intern Med 1990;112(10): 750–757.
32. O'Riordan TG, Smaldone G. Exposure of health-care workers to aerosolized pentamidine. Chest 1992;101(16):1494–1499.
33. McIvor RA, Lee-Pack LR, Chan CK. Occupational exposure and pulmonary function in health care workers in an aerosol pentamidine clinic. Chest 1994;106(3):980–981.
34. Cross CE. Amphotericin B aerosol for transiently immunocompromised hosts: reasonably safe, but does it matter? Chest 1995;108(3): 599–601.
35. Hertenstein B, Kern WV, Schmeiser T, Stefanic M, Bunjes D, Wiesneth M, et al. Low incidence of invasive fungal infections after bone marrow transplantation in patients receiving amphotercin B inhalations during neutropenia. Ann Hematol 1994;68(1):21–26.
36. Beyer J, Barzen G, Risse G, Weyer C, Miksits K, Dullenkopf K, et al. Aerosol amphotericin B for prevention of invasive pulmonary aspergillosis. Antimicrob Agents Chemother 1993;37(6):1367–1369.
37. Reichenspurner H, Gamberg P, Nitschke M, Valentine H, Hunt S, Oyer PE, et al. Significant reduction in the number of fungal infections after lung, heart-lung, and heart transplantation using aerosolized amphotercin B prophylaxis. Transplantation Proceedings 1997; 29(1-2):627–628.
38. Tsourounis C, Guglielmo BJ. Aerosolized amphotercin B in prophylaxis of pulmonary aspergillosis. Ann Pharmacother 1996;30(10): 1175–1176.
39. McEvoy GK, editor. American Hospital Formulary Service. Drug Information 1998; Ribavirin. American Society of Health System Pharmacists. Bethesda; 1998: 506–51.
40. Ottolini MG, Hemming VG. Prevention and treatment recommendations for respiratory syncytial virus infection: background and clinical experience 40 years after discovery. Drugs 1997;54:867–884.
41. Smith DW, Frankel LR, Mathers LH, et al. A controlled trial of aerosolized ribavirin in infants receiving mechanical ventilation for severe respiratory syncytial virus infection. N Engl J Med 1991; 325(1):24–29.
42. Meert KI, Sarnaik AP, Gelmini MJ, Lieh-Lai MW. Aerosolized ribavirin in mechanically ventilated children with respiratory syncytial virus lower respiratory disease: a prospective, double-blind, randomized trial. Crit Care Med 1994;22(4):566–572.
43. Gilbert BE and Knight V. Ribavirin aerosol as the treatment for influenza. Drugs Today 1990;26:195–205.
44. Sullivan KM. Health impact of influenza in the United States. Pharmaco Eco 1996;9:(Suppl 3):26–33.
45. Hayden FG, Osterhaus AD, Treanor JJ, Fleming DM, Aoki FY, Nicholson KG, et al. Efficacy and safety of the neuraminidase inhibitor zanamivir in the treatment of influenzavirus infections. GG167 Influenza Study Group. N Engl J Med 1997;337(13):874–880.

Comparing Inhaled Corticosteroids

Gene L Colice MD

Introduction
Therapeutic Indications for Inhaled Corticosteroids
Methods for Comparing Inhaled Corticosteroids
Potency
Pharmacokinetics/Pharmacodynamics
Clinical Trials
Effects of Inhalation Delivery Device
Summary
[Respir Care 2000;45(7):846–853] *Key words: corticosteroid, inhaled, asthma, anti-inflammatory.*

Introduction

At present in the United States, there are 5 different corticosteroids available for use via the inhalation route (Table 1). These are beclomethasone dipropionate (BDP), budesonide, flunisolide, fluticasone propionate, and triamcinolone acetonide. Extensive information has been compiled on the differences in pharmacologic profiles among these products. Both in vivo and in vitro testing suggests that these 5 inhaled corticosteroids may have clinically relevant differences in potency. Consequently, asthma management guidelines indicate that equal doses of these products should not be expected to have equivalent clinical effects.[1] Dosing regimens must be adjusted for the severity of asthma when switching from use of one inhaled corticosteroid to another (Table 2).

Another important distinguishing feature among these products is the delivery device used for inhalation administration. Three of these inhaled corticosteroids (BDP, flunisolide, and triamcinolone acetonide) are marketed in metered-dose inhalers (MDIs), one (budesonide) is available only in a dry powder inhaler (DPI), and one (fluticasone propionate) is available in both an MDI and a DPI form. The inhaled corticosteroids currently available in MDIs are formulated in the traditional chlorfluorocarbon (CFC) propellants. The United States Food and Drug Administration (FDA) is currently reviewing new drug applications for several inhaled corticosteroids reformulated in non-CFC propellants (BDP, fluticasone, and triamcinolone acetonide). A new drug application has been submitted to the FDA for an inhaled corticosteroid (fluticasone) reformulated in a new type of DPI. In addition, a novel inhaled corticosteroid (mometasone furoate) formulated in a DPI is also being evaluated by the FDA.

As a result of these pharmaceutical development efforts, conceivably within the near future, respiratory clinicians will have 6 different inhaled corticosteroids in various inhalation delivery devices available for use. Comparing these inhaled corticosteroids will be an important concern for health care professionals in choosing the most appropriate treatment for patients with respiratory disease.

Therapeutic Indications for Inhaled Corticosteroids

In the United States, the only currently approved indication for inhaled corticosteroids is as prophylactic therapy for the maintenance treatment of asthma. There has been considerable interest in using inhaled corticosteroids for other diseases, most notably chronic obstructive pulmonary disease and sarcoidosis. Clinical data obtained from large trials show that the use of inhaled corticosteroids in chronic obstructive pulmonary disease may confer small advantages in preserving lung function[2] and reducing ex-

Gene L Colice MD is affiliated with Pulmonary, Critical Care, and Respiratory Services, Washington Hospital Center, Washington DC.

A version of this paper was presented by Dr Colice during the New Horizons Symposium, "Clinical Pharmacology of Inhaled Agents for the Respiratory Care Clinician," at the American Association for Respiratory Care's 45th International Respiratory Congress, December 14, 1999, in Las Vegas, Nevada.

Correspondence: Gene L Colice MD, Pulmonary, Critical Care, and Respiratory Services, Washington Hospital Center, 110 Irving Street NW, Washington DC 20010.

Table 1. Currently Approved Inhaled Corticosteroids

Generic name	Beclomethasone Dipropionate	Budesonide	Flunisolide	Fluticasone Propionate	Fluticasone Propionate	Triamcinolone Acetonide
Brand name (manufacturer)	Beclovent (Glaxo Wellcome) Vanceril and Vanceril DS (Schering Plough)	Pulmicort Turbuhaler (Astra Zeneca)	Aerobid and Aerobid-M (Forest)	Flovent (Glaxo Wellcome)	Flovent Rotadisk (Glaxo Wellcome)	Azmacort (Rhône-Poulenc Rorer)
Dosage form	MDI 42 μg/puff ex-actuator (84 μg/puff for the double-strength product)	DPI 200 μg/dose	MDI 250 μg/puff ex-actuator	MDI 44, 110, or 220 μg/puff ex-actuator	DPI 50, 100, or 250 μg/dose	MDI with built-in spacer 100 μg/puff ex-spacer
Recommended adult daily dose	252–840 μg 2 puffs tid–10 puffs bid (half the number of puffs for the double-strength product)	400–1,600 μg 1 dose bid–4 doses bid (stable patients can be maintained on 1 dose of 200 μg/d)	1,000–2,000 μg 2 puffs bid–4 puffs bid	176–1,760 μg 2 puffs bid (44)–4 puffs bid (220)	200–2,000 μg 2 doses bid (50)–4 doses bid (250)	600–1,600 μg 2 puffs tid–8 puffs bid
Recommended pediatric daily dose	Age 6–12 132–420 μg 1 puff tid–5 puffs bid	Age 6–12 400–800 μg 1 dose bid–2 doses bid (stable patients can be maintained on 1 dose of 200 μg/d)	Age 6–15 1,000 μg 2 puffs bid	Not approved for this age group	Age 4–11 100–200 μg 1 dose bid (50)–2 doses bid (50)	Age 6–12 300–1,200 μg 1 puff tid–6 puffs bid

MDI = metered-dose inhaler. DPI = dry powder inhaler.

Table 2. Doses of Inhaled Corticosteroids Recommended by the National Asthma Education and Prevention Program for Adults by Severity of Asthma*

	Beclomethasone Dipropionate	Budesonide	Flunisolide	Fluticasone Propionate (MDI)	Fluticasone Propionate (DPI)	Triamcinolone Acetonide
Low dose for mild, persistent	168–504 μg/d	200–400 μg/d	500–1,000 μg/d	88–264 μg/d	100–300 μg/d	400–1,000 μg/d
Medium dose for moderate, persistent	504–840 μg/d	400–600 μg/d	1,000–2,000 μg/d	264–660 μg/d	300–600 μg/d	1,000–2,000 μg/d
High dose for severe, persistent	> 840 μg/d	> 600 μg/d	> 2,000 μg/d	> 660 μg/d	> 600 μg/d	> 2,000 μg/d

*These recommendations are taken from the Expert Panel II report[1] and do not necessarily conform to FDA-approved dosing.[1]
MDI = metered-dose inhaler. DPI = dry powder inhaler.

acerbation rates.[3] However, it is unclear whether these benefits warrant the cost, inconvenience, and potential risks of long-term treatment of chronic obstructive pulmonary disease with inhaled corticosteroids. Although preliminary data suggested that inhaled corticosteroids might be effective in the treatment of sarcoidosis,[4] recent work has not been able to confirm this benefit.[5]

By United States and international guidelines on asthma management,[1,6] inhaled corticosteroids are accepted to be the most useful medication currently available for the control of persistent asthma symptoms. The beneficial effects of inhaled corticosteroids in asthma relate to the basic pathophysiology of this disease and the known pharmacologic effects of this class of drugs. Asthma is a disease clinically recognized by airway hyperresponsiveness, but it is really an inflammatory airway disease. The inflammation extends from the large airways to the small airways.[7,8] Airway inflammation can be found at the first presentation of patients with asthma symptoms,[9] and is evident even in patients with mild, intermittent symptoms.[10]

A characteristic histologic feature of inflammation in asthma is infiltration of airway walls by eosinophils. A more recently recognized feature of inflammation in asthma is remodeling of airway walls, specifically, thickening of the lamina reticularis just below the basement membrane of the airway epithelium.[11] Airway remodeling may contribute to chronic air flow obstruction in asthma.

Corticosteroids have direct inhibitory effects on several of the inflammatory cells implicated in the pathogenesis of asthma.[12] These drugs reduce the number of circulating eosinophils, by either a direct action at the bone marrow level or through reducing the levels of cytokines known to be required for eosinophil survival. Mucosal mast cell numbers also decrease with corticosteroid treatment, again possibly because of reduction in the cytokines and growth factors necessary for mast cell survival. Corticosteroids directly inhibit release of inflammation mediators from lymphocytes, alveolar macrophages, and airway epithelial cells. In addition, corticosteroids are known to reduce mucus secretion in airways, possibly by a direct inhibitory effect on submucosal gland cells.

The molecular mechanisms by which corticosteroids exert their anti-inflammatory effects are not entirely understood. Corticosteroids are known to bind with cytoplasmic receptors. The corticosteroid-receptor complexes translocate to the nucleus, bind to recognition sequences on corticosteroid responsive genes, and directly affect transcription of genomic content. However, the anti-inflammatory effects of corticosteroids probably cannot be explained entirely by their interactions with corticosteroid response genes. Corticosteroids were recently found to interact with other cytoplasmic factors, such as activator protein-1 and nuclear factor-κB, which also affect genomic transcription. It is becoming more apparent that corticosteroids have a complex effect on intracellular function. Whether the cumulative effects of corticosteroids on genetic transcription are an increase in cellular anti-inflammatory protein synthesis, a decrease in inflammatory protein synthesis, or a combination of both is not clear.

In clinical practice, inhaled corticosteroids effectively reduce airway inflammation in asthma patients. Improvements in lung function and reduction of asthma symptoms with the use of inhaled corticosteroids have been directly related to a decrease in airway inflammation.[13] The long-term use of inhaled corticosteroids has been shown to reduce both airway inflammation and secondary airway remodeling.[14] The fundamentally important role of inhaled corticosteroids in treating asthma has been demonstrated by several studies, which showed that the maximum beneficial effect is achieved with early use of these drugs. For example, delaying use by relying on bronchodilators alone to manage symptoms reduces the improvement in lung function potentially achievable with inhaled corticosteroids.[15,16]

In the treatment of asthma, corticosteroids may be administered in a variety of ways other than the inhaled route, including orally or systemically as either an intravenous or intramuscular injection. In severe cases of asthma, oral or systemic administration of corticosteroids is preferred. However, potentially serious disadvantages of oral and systemic administration of corticosteroids include the risk of systemic adverse effects. With prolonged use of oral and systemic corticosteroids comes the risk of suppression of the hypothalamic-pituitary adrenal axis, inhibition of growth in pediatric patients, and osteoporosis in adults, skin thinning, easy bruisability, ocular cataracts, abnormalities in carbohydrate and lipid metabolism, change in body habitus, and mood disorders. An important advantage of inhaled corticosteroids is that they have been shown to have a topical anti-inflammatory effect.[17] Consequently, inhaled corticosteroids achieve and maintain beneficial anti-inflammatory effects with much lower total daily doses and much less risk of serious adverse effects than oral or systemic corticosteroids.

Methods for Comparing Inhaled Corticosteroids

Potency

The term "potency" refers to the strength of the physiologic or pharmacologic response to a known concentration of a drug. Although potency implies a bearing on clinical efficacy, this may not always be the case. The actual relationship between potency and clinical efficacy is complex, because the physiologic or pharmacologic test used in assessing potency may not accurately reflect the disease pathophysiology. Inhaled corticosteroids provide a good example of the difficulties encountered in relating potency to clinical efficacy. The most commonly used test to assess the potency of inhaled corticosteroids is the MacKenzie skin blanching test. The corticosteroid to be tested is formulated in a solution and placed on the skin for several hours. The degree of blanching or whitening of the underlying skin is used as the measure of potency. However, skin blanching reflects vasoconstriction, which is not a prominent feature of asthma pathophysiology. Furthermore, the vascular structure of the skin is substantially different than that of the lung. Relative potencies of the 5 currently available inhaled corticosteroids have been measured using the MacKenzie skin blanching test (Table 3), but should only be interpreted in the context of clinical trial results.[18]

Other methods for estimating potency of inhaled corticosteroids involve measuring the receptor binding affinity and the receptor binding half-life. A drug that binds more avidly to receptors for longer time periods might be expected to be more effective. There are limitations to these tests, however. The cells used for in vitro testing of re-

Table 3. Relative Topical Potencies and Receptor Binding Characteristics of Currently Available Inhaled Corticosteroids

	Beclomethasone Dipropionate	Budesonide	Flunisolide	Fluticasone Propionate	Triamcinolone Acetonide
MacKenzie skin blanching test*	600	980	330	1,200	390
Receptor binding affinity*	0.4	9.4	1.8	18.0	3.6
Receptor binding half-life (hours)	Not known	5.1	3.5	10.5	3.9

*Relative to dexamethasone with a value of 1.

ceptor binding affinity and receptor binding half-life might not accurately reflect the binding affinities of relevant inflammatory cells such as eosinophils and mast cells. A more fundamental difficulty with this approach is apparent from the emerging view of the molecular mode of action of corticosteroids. It is becoming clear that corticosteroids are interacting with cells in more complex ways than can be accounted for by receptor binding alone, as discussed above. Accepting these difficulties with relating binding affinity and half-life to cellular effects, the known binding characteristics of inhaled corticosteroids (see Table 3) should be interpreted cautiously.[18]

More recently, attempts have been made to relate in vitro corticosteroid receptor binding affinity to transcriptional activity of genes known to be controlled by the corticosteroid receptor.[19] As the genes responsible for the anti-inflammatory effects of corticosteroids become better understood, this approach may be very useful in relating in vitro measures of potency to clinical measures of efficacy. Another approach to comparing the potency of inhaled corticosteroids is to measure histamine release from basophils, eosinophil viability, and eicosanoid release from airway epithelial cells after prolonged culture with the various drugs.[20,21] The advantage to this approach is the use of cells accepted to be intimately related to the pathogenesis of asthma.

Pharmacokinetics/Pharmacodynamics

The usual approaches to assessing the pharmacokinetic profile of a drug rely on measuring serum concentrations over time and calculating such factors as peak serum concentration, time to peak serum concentration, serum half-life, and integrated serum concentration over time (also known as the area-under-the-curve of serum concentration). Unfortunately, these standard pharmacokinetic assessments provide little insight into differences among inhaled corticosteroids, because the efficacy of these drugs is related to their topical anti-inflammatory effects and not their serum concentrations. For inhaled corticosteroids, their pharmacodynamic profile, which is the relationship between drug dose and drug effect, relates to the intrapulmonary handling of the inhaled drug. Recent work indicates that for some inhaled corticosteroids there is a dissociation between serum concentration of the drug and concentration in lung tissue. Fluticasone propionate has been shown to be retained in lung tissue for much longer than is evident from serum concentrations.[22] The implication of this finding is that the topical anti-inflammatory effect will persist for much longer than the risk of systemic adverse effects.

Because it is difficult to estimate topical airway anti-inflammatory effects from serum concentrations of an inhaled corticosteroid, an alternative method for comparing inhaled corticosteroids has been proposed. This approach is based on calculating the lung and systemic biovailability profiles of the various products. The bioavailability of a product relates the integrated serum concentration of a drug over time to the dose administered. Bioavailability of a product depends on the method of administration. Intravenous administration is typically used to measure systemic bioavailability and is an accepted reference standard for drugs administered via inhalation. Relating bioavailability after inhalation delivery to systemic bioavailability allows calculation of lung bioavailability. High lung bioavailability relative to systemic bioavailability indicates that more of the drug reached the systemic circulation via the lungs, and, consequently, provided beneficial topical anti-inflammatory effects.

Estimating the lung-to-systemic bioavailability ratio provides a basis for understanding the therapeutic index of an inhaled corticosteroid. The therapeutic index quantifies the relationship between benefits and risks of administering any drug. The concept of relative therapeutic indices is probably most easily understood by comparing the use of inhaled corticosteroids and oral/systemic corticosteroids in asthma. The beneficial effect of administering corticosteroids by any route is the anti-inflammatory effect. However, the benefits of an inhaled corticosteroid in treatment of asthma are clearly the topical anti-inflammatory effects. In other words, by administering the drug directly to the airways (the site of inflammation) the dose can be kept sufficiently low that systemic anti-inflammatory effects (and, presumably, systemic adverse effects) are avoided. Oral and systemic corticosteroids reach

the lung secondarily through the systemic circulation and cause both systemic and local (respiratory tract) anti-inflammatory effects. However, the risks of systemic adverse effects is, obviously, much greater, because the corticosteroid reaches the systemic circulation through nonpulmonary routes, either the gastrointestinal tract or the venous system. In general, inhaled corticosteroids have a more favorable therapeutic index than oral or systemic corticosteroids because the beneficial anti-inflammatory effects are achieved with much less risk of systemic adverse effects. Conceptually, inhaled corticosteroids can be viewed as having a high lung bioavailability and a low systemic bioavailability (ie, the products are delivered directly to the lung and little gets into the systemic circulation). Oral and systemic corticosteroids have a relatively low lung bioavailability (only a portion reaches the lungs and most is distributed throughout the rest of the body) but a high systemic bioavailability.

The therapeutic index of various inhaled corticosteroids can be compared in a similar way. Products with the most favorable therapeutic index have most of the drug entering the body through the lungs (ie, high lung bioavailability) and only a small amount reaching the systemic circulation through nonpulmonary routes (ie, low systemic bioavailability). This type of comparison is possible because the pharmaceutical industry has developed inhaled corticosteroids that differ substantially in their lung deposition and metabolic characteristics. For the inhaled corticosteroids that have been commercially available for more than 5–10 years, only a small percentage of the drug released from the delivery device actually reaches the lower respiratory tract.[23] Most of the aerosolized particles released from the delivery device and carrying drug actually impact on the tongue or the posterior oropharynx. These particles are subsequently swallowed; swallowed drug may eventually reach the systemic circulation after being absorbed in the gastrointestinal tract and passing through the hepatic circulation. The therapeutic index is still favorable compared to oral and systemic corticosteroids, but is not ideal, because drug reaching the systemic circulation through the gastrointestinal tract may cause systemic adverse effects with minimal contribution of airway anti-inflammatory benefit.

Recognizing the historic limitations of delivering inhaled corticosteroids to the airways, the pharmaceutical industry took two different approaches to improve the therapeutic index of these products. The first approach was to increase the metabolism of absorbed drug by the liver so that, even though the drug might have poor lung deposition characteristics, any swallowed drug would be broken down in the liver and thus unlikely to reach the systemic circulation. Another approach was to improve the lung deposition characteristics of the inhaled corticosteroid. The inhaled corticosteroid currently available with the best lung deposition profile is budesonide, but even with this product only about 25–30% of the aerosolized drug reaches the lungs. A newer product, though, has much improved lung deposition characteristics: approximately 55–60% of the ex-actuator dose of BDP formulated in a non-CFC propellant reaches the lower respiratory tract.[24] The majority of drug with excellent lung deposition characteristics that reaches the systemic circulation has passed through the lungs and provided topical anti-inflammatory benefits.

An estimate of the lung-to-systemic bioavailability ratio is a surrogate estimate of the therapeutic index of an inhaled corticosteroid. The greater the proportion of drug reaching the systemic circulation through the lungs (lung bioavailability) relative to total systemic bioavailability of drug, the greater the topical anti-inflammatory benefits relative to the risks of systemic adverse effects. Estimates of the lung-to-systemic bioavailability ratio suggest that inhaled corticosteroids that are either metabolized extensively by the liver (such as fluticasone) or have excellent lung deposition characteristics (such as the new BDP product) will be preferred (Table 4).

Clinical Trials

Inherent in our understanding that inhaled corticosteroids provide their benefits through topical anti-inflammatory effects is an appreciation that surrogate measures such

Table 4. Estimates of the Lung to Systemic Bioavailability Ratios for Inhaled Corticosteroids*

Product	% Dose Deposited in the Lungs	% Dose Reaching the Systemic Circulation after Absorption from the Gastrointestinal Tract	Lung/Systemic Bioavailability Ratio
BDP via CFC propellant	5.5	14.7	0.27
BDP via non-CFC propellant	56.1	5.5	0.92
Budesonide via MDI	15	7.7	0.66
Budesonide via DPI	30	5.3	0.85
Fluticasone propionate via DPI	12	0.6	0.95

*Data from personal communication with 3M Pharmaceuticals, St Paul, Minnesota, 1999.
BDP = beclomethasone dipropionate. CFC = chlorofluorocarbon. MDI = metered-dose inhaler. DPI = dry powder inhaler.

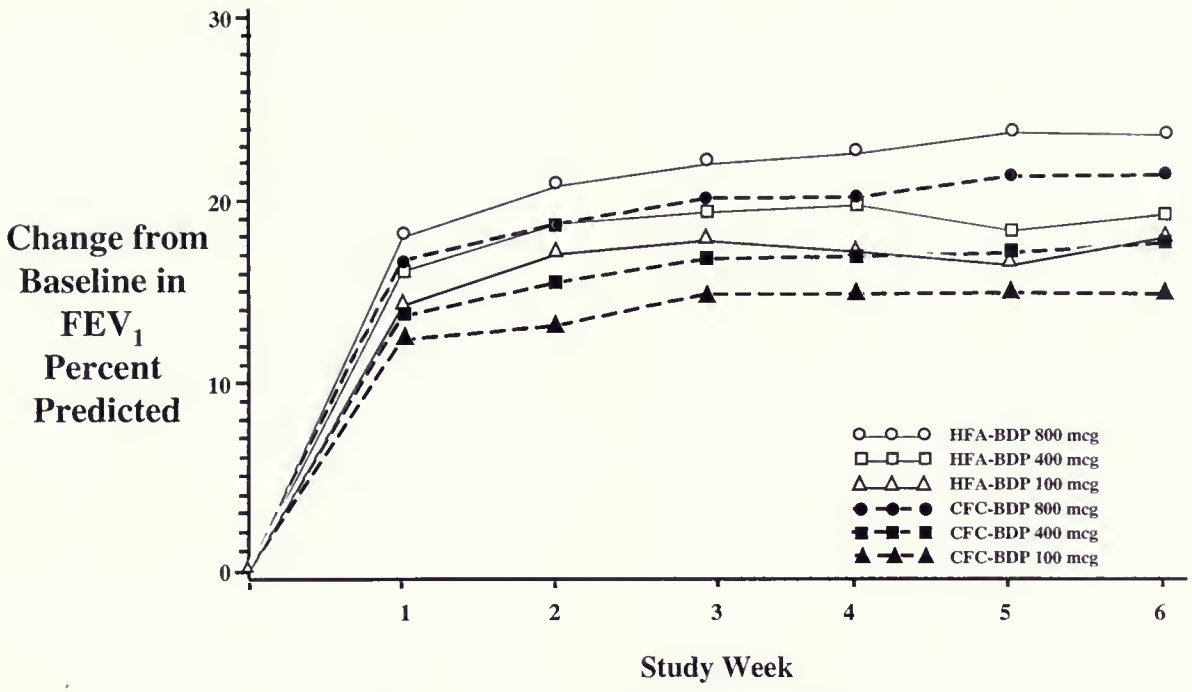


Fig. 1. The change from baseline in forced expiratory volume in the first second (FEV_1) percent of predicted is shown for the study comparing beclomethasone dipropionate (BDP) formulated in chlorofluorocarbon (CFC) propellant (filled circles, squares, and triangles) with BDP formulated in a non-CFC propellant (hydrofluoroalkane [HFA]) (open circles, squares, and triangles) over the 6 weeks of the study. Three different doses of each product were used. Note that there was increasing benefit for each product as dose was increased. Also, at each dosing level there was greater benefit from the non-CFC BDP product. (Adapted from Reference 25.)

as potency and estimates of lung and systemic bioavailability will not be true measures of the differences among inhaled corticosteroids. The most useful and clinically relevant method for comparing inhaled corticosteroids should be based on patient trials. However, historically, the use of clinical trials to compare inhaled corticosteroids has not been successful,[12] because of a combination of factors, particularly related to two features of study design. To compare inhaled corticosteroids, it is first essential to include patients who are known to be responsive to inhaled corticosteroids. It is also critical to include multiple doses of the inhaled corticosteroids being compared to demonstrate dose response (ie, increasing effect with increasing dose). Only by demonstrating a dose response can the effects of two different inhaled corticosteroids be compared.

A recent study demonstrated that with the proper study design the clinical efficacy of two different inhaled corticosteroids can be distinguished. The study compared the currently available BDP product formulated in CFC propellant with a BDP product formulated in a non-CFC propellant. It was hypothesized that the BDP in the non-CFC propellant would have greater clinical efficacy because it had better lung deposition characteristics. The study design required that asthma patients using inhaled corticosteroids undergo an inhaled corticosteroid washout phase. Only patients who had a decrease in lung function and an increase in asthma symptoms with inhaled corticosteroid washout were entered into the study. This requirement ensured that the study population was clearly responsive to inhaled corticosteroids. The study design also included 3 different doses of each of the 2 products. The statistical analysis required that increasing benefit be found with increasing doses of each product before the two products could be compared. The results demonstrated (Fig. 1) that this approach was successful in showing that the BDP product formulated in the non-CFC propellant (with better lung deposition characteristics) was indeed more effective in improving lung function and controlling asthma symptoms.[25] This improvement in clinical effect was achieved without compromising systemic safety.[26]

Effects of Inhalation Delivery Device

There has been tremendous interest, both within the pharmaceutical industry and academia, in the development of new types of inhalation delivery devices. At present there are two basic types of inhalation delivery devices commercially available for use with inhaled corticosteroids in the United States: the MDI and the DPI. There are important differences between the two types of DPIs currently available in the United States. The differences be-

tween MDIs and DPIs are further compounded by the common recommendation to use spacer devices with MDIs but not with DPIs. Also, there is considerable variability in pharmaceutic profile (ie, the medication delivery and the medication particle size distribution) among the various inhalation delivery devices. Little research is currently available on the implications of these differences on clinical efficacy; most studies concentrate on the risk of systemic adverse effects with use of different inhalation delivery devices and provide no information on any potential benefits.[27]

One particularly unfortunate aspect of the development of new inhalation delivery devices has been a marketing emphasis on the ease of use of these products, with little data on how this might affect actual patient use. The implication that an easier-to-use product might improve patient adherence with regular use of their inhaled corticosteroids must be substantiated by clinical trial data. Consequently, it is premature to compare either different inhaled corticosteroids or the same inhaled corticosteroid on the basis of type of inhalation delivery device. Fortunately, the respiratory care practicioner can choose among a variety of inhalation delivery devices, based on a needs assessment of the individual patient for the administration of inhaled corticosteroids.

Summary

There are currently available 5 different inhaled corticosteroids, in a variety of different inhalation delivery devices. In the near future there will certainly be more inhaled corticosteroids in newer inhalation delivery devices available in the United States. Tremendous amounts of information will be made available about the relative advantages and disadvantages of these new products. Most of this information will relate to measures of potency, pharmacokinetic profiles, and technical issues about the ease of use. The respiratory care practicioner should be aware that estimating the clinical benefits from the topical anti-inflammatory effects of these newer products will be difficult to determine from this information. Also difficult to understand will be the effects of easier to use inhalation delivery devices on patient adherence to prescribed inhaled cortiocosteroid dosing regimens. Information from well designed clinical trials should be the basis for comparing presently available and newly developed inhaled corticosteroids.

REFERENCES

1. National Asthma Education and Prevention Program. Expert Panel Report 2: Guidelines for the diagnosis and management of asthma. Bethesda, 1997; National Institutes of Health, NHLBI, NIH Publication No. 97–4051. Available at www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed June 6, 2000.
2. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, Ohlsson SV. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999;340(25): 1948–1953.
3. Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomised placebo-controlled trial of inhaled fluticasone propionate in patients with chronic obstructive pulmonary disease. Lancet 1998;351(9105):773–780.
4. Alberts C, van der Mark TW, Jansen HM. Inhaled budesonide in pulmonary sarcoidosis: a double-blind, placebo-controlled study. Dutch Study Group on Pulmonary Sarcoidosis. Eur Respir J 1995; 8(5):682–688.
5. Pietinalho A, Tukiainen P, Haahtela T, Persson T, Selroos O. Oral prednisolone followed by inhaled budesonide in newly diagnosed pulmonary sarcoidosis: a double-blind, placebo-controlled multicenter study. Finish Pulmonary Sarcoidosis Study Group. Chest 1999; 116(2):424–431.
6. The British guidelines on asthma management: 1995 review and position statement. The British Thoracic Society, The National Asthma Campaign, The Royal College of Physicians of London in association with the General Practitioner in Asthma Group, the British Association of Accident and Emergency Medicine, the British Paediatric Respiratory Society and the Royal College of Paediatrics and Child Health.Thorax 1997;52 (Suppl 2):S1–S20.
7. Hamid Q, Song Y, Kotsimbos TC, Minshall E, Bai TR, Hegele RG, Hogg JC. Inflammation of small airways in asthma. J Allergy Clin Immunol 1997;100(1):44–51.
8. Carroll N, Elliot J, Morton A, James A. The structure of large and small airways in nonfatal and fatal asthma. Am Rev Respir Dis 1993;147(2):405–410.
9. Laitinen LA, Laitinen A, Haahtela T. Airway mucosal inflammation even in patients with newly diagnosed asthma. Am Rev Respir Dis 1993;147:697–704.
10. Vignola AM, Chanez P, Campbell AM, Souques F, Lebel B, Enander I, Bousquet J. Airway inflammation in mild intermittent and in persistent asthma. Am J Respir Crit Care Med 1998;157(2):403–409.
11. Busse W, Elias J, Sheppard D, Banks-Schlegel S. Airway remodeling and repair. Am J Respir Crit Care Med 1999;160(3):1035–1042.
12. Barnes PJ, Pedersen S, Busse WW. Efficacy and safety of inhaled corticosteroids: new developments (review). Am J Respir Crit Care Med 1998;157(3 Pt 3):S1–S53.
13. Djukanovic R, Wilson JW, Britten KM, Wilson SJ, Wells AF, Roche WR, et al. Effect of an inhaled corticosteroid on airway inflammation and symptoms in asthma. Am Rev Respir Dis 1992;145(3):669–674.
14. Trigg CJ, Manolitsas ND, Wang J, Calderon MA, McAulay A, Jordan SE, et al. Placebo-controlled immunopathologic study of four months of inhaled corticosteroids in asthma. Am J Respir Crit Care Med 1994;150(1):17–22.
15. Overbeek SE, Kerstjens HAM, Bogaard JM, Mulder PGH, Postma DS. Is delayed introduction of inhaled corticosteroids harmful in patients with obstructive airways disease (asthma and COPD)? The Dutch CNSLD Study Group. Chest 1996;110(1):35–41.
16. Selroos O, Pietinalho A, Lofroos AB, Riska H. Effect of early vs late intervention with inhaled corticosteroids in asthma. Chest 1995; 108(5):1228–1234.
17. Lawrence M, Wolfe J, Webb DR, Chervinsky P, Kellerman D, Schaumberg JP, Shah T. Efficacy of inhaled fluticasone propionate in asthma results from topical and not systemic activity. Am J Respir Crit Care Med 1997;156(3 Pt 1):744–751.
18. Kelly HW. Establishing a therapeutic index for the inhaled corticosteroids. J Allergy Clin Immunol 1998;102(4 Pt 2):S36–S51.

19. Smith CL, Kreutner W. In vitro glucocorticoid receptor binding and transcriptional activation by topically active glucocorticoids. Arzneimittelforschung 1998;48(9):956–960.
20. Stellato C, Atsuta J, Bickel CA, Schleimer RP. An in vitro comparison of commonly used topical glucocorticoid preparations. J Allergy Clin Immunol 1999;104(3 Pt 1):623–629.
21. Aksoy MO, Li X, Borenstein M, Yi Y, Kelsen SG. Effects of topical corticosteroids on inflammatory mediator-induced eicosanoid release by human airway epithelial cells. J Allergy Clin Immunol 1999; 103(6):1081–1091.
22. Esmailpour N, Hogger P, Rabe KF, Heitmann U, Nakashima M, Rohdewald P. Distribution of inhaled fluticasone propionate between human lung tissue and serum in vivo. Eur Respir J 1997;10(7):1496–1499.
23. Hochhaus G, Mollmann H, Derendorf H, Gonzalez-Rothi R. Pharmacokinetic/pharmacodynamic aspects of aerosol therapy using glucocorticoids as a model. J clin Pharmacol 1997;37(10):881–892.
24. Leach CL, Davidson PJ, Boudreau RJ. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. Eur Respir J 1998;12(6):1346–1353.
25. Busse WW, Brazinsky S, Jacobson K, Stricker W, Schmitt K, Vanden Burgt J, et al. Efficacy response of inhaled beclomethasone dipropionate in asthma is proportional to dose and is improved by formulation with a new propellant. J Allergy Clin Immunol 1999;104(6): 1215–1222.
26. Harrison LI, Colice GL, Donnell D, Soria I, Dockhorn R. Adrenal effects and pharmacokinetics of CFC-free beclomethasone dipropionate: a 14-day dose-response study. J Pharm Pharmacol 1999;51(3): 263–269.
27. Wales D, Makker H, Kane J, McDowell P, O'Driscoll BR. Systemic bioavailability and potency of high-dose inhaled corticosteroids: a comparison of four inhaler devices and three drugs in healthy adult volunteers. Chest 1999;115(5):1278–1284.

Inhaled Adrenergic Bronchodilators: Historical Development and Clinical Application

Joseph L Rau PhD RRT FAARC

Introduction
Historical Perspective
Differentiation of Adrenergic Receptors
Development of β Agonist Bronchodilators
β Agonists as Stereoisomers
Specific Adrenergic Bronchodilators
Adverse Effects With β Agonists
General Adverse Effects
Tolerance to β Agonists
The "Asthma Paradox"
Is the S-isomer Inactive?
β Agonists and the National Asthma Education and Prevention Program Guidelines
Summary

[Respir Care 2000;45(7):854–863] *Key words: beta agonist, adrenergic, bronchodilator, asthma, isomer, inhaled, aerosol.*

Introduction

Beta (β) agonist bronchodilators represent the largest single drug group among the various classes of inhaled therapeutic aerosol drugs. They also represent one of the most interesting examples of drug class development, illustrating the gradual unfolding of receptor theory concomitant with synthesis of improved drug molecules.

Historical Perspective

Ephedrine, a sympathomimetic agent contained in the plant Ephedra vulgaris, was known to the Chinese as early as 3000 BC and was used to make the drug ma huang for the treatment of asthma.[1] In the late 1800s, adrenal extracts began to be investigated and used for their vasoconstricting properties in the treatment of rhinitis and conjunctivitis, as well as asthma.[2,3] In 1899, epinephrine received its name from Abel and was soon isolated and synthesized independently by Stolz and Dakin.[4] The term "adrenaline" may have been first coined by Wilson in 1901 to refer to epinephrine.[5] In 1903, epinephrine was used by both the oral and subcutaneous routes to treat asthmatics, with subcutaneous delivery found to be more effective than oral.[6] Asthma was initially thought to be caused by vasodilation, and the efficacy of epinephrine was explained by its vasoconstricting property. It was for this reason that cocaine, a potent vasoconstrictor, had been used beginning around 1800 in asthma and rhinitis. However, in 1907 Kahn demonstrated the bronchodilator effect of epinephrine.[7] Following this, both the vasoconstrictive and bronchodilator effects of epinephrine were thought to be the basis for its beneficial effect in asthma. Barger and Dale reported the use of epinephrine as an aerosol in 1910.[8] Not until 30 years later did isoproterenol appear for bronchodilator use, and isoetharine, synthesized as early as 1936, was first reported in treating asthma in 1951.[9]

Joseph L Rau PhD RRT FAARC is affiliated with Cardiopulmonary Care Sciences, Georgia State University, Atlanta, Georgia.

A version of this paper was presented by Dr Rau during the New Horizons Symposium, "Clinical Pharmacology of Inhaled Agents for the Respiratory Care Clinician," at the American Association for Respiratory Care's 45th International Respiratory Congress, December 14, 1999, in Las Vegas, Nevada.

Correspondence: Joseph L Rau PhD RRT FAARC, Cardiopulmonary Care Sciences, Georgia State University, University Plaza, Atlanta GA 30303-3083. E-mail: jrau@gsu.edu.

Today, epinephrine is still available for use as a bronchodilator aerosol. Of a total of 10 drugs in the adrenergic bronchodilator group currently available as orally inhaled aerosols in the United States, nine are derivatives of epinephrine. The development of adrenergic agents has proceeded apace, with continuously improving knowledge of the receptors stimulated by these drugs. In particular, the β adrenergic receptor is now fully identified and its function clarified in detail.

Differentiation of Adrenergic Receptors

Originally, identification of adrenergic receptors was inferred indirectly from the different effects of individual adrenergic drugs. Although such drugs as epinephrine, isoproterenol, and phenylephrine were all sympathomimetic, different physiologic effects were observed among these agents. In 1948, Raymond Ahlquist published his classic paper proposing that there were two distinct adrenergic receptors, α and β.[10] The α receptor was associated with excitatory functions, with the exception of the intestine, where an inhibitory effect was observed. The β receptor was associated with inhibition, with the exception of the myocardium, where an excitatory effect was observed. This concept of two fundamental types of receptors mediating the effects of the sympathetic nervous system contrasted with the previously espoused view of Cannon and Rosenbleuth of two excitatory and inhibitory substances, sympathin E and sympathin I, as adrenergic mediators.[10]

Subsequently, Lands et al further subdivided the β receptor into two subtypes, denoted as β-1 and β-2.[11] β-1 receptors increase cardiac rate and force, relax intestinal smooth muscle, and account for the excitatory effects seen with drugs such as isoproterenol. β-2 receptors mediate the relaxation of bronchial, uterine, and vascular smooth muscle. The location of β-2 receptors within the airway, combined with localized targeted delivery of inhaled β-2 agonists to the airway, provides an optimal method of bronchodilation in reversible air flow obstruction.

The human β receptor has been cloned and studied; it consists of 413 amino acids, and is a member of the 7-transmembrane family of receptors.[12] β receptors have now been subdivided into three groups: β-1, β-2, and β-3, which are identified predominantly in cardiac, airway smooth muscle, and adipose tissue, respectively.[13] The β receptor polypeptide has an extracellular terminus, loops 7 times through the cell membrane lipid bilayer, and has an intracellular terminal carboxyl group, as illustrated in Figure 1.[14]

Viewed three-dimensionally, the membrane-spanning loops of the β receptor form a cylindrical or barrel-shaped structure. β agonists bind inside of the barrel, about 30–40% of the way into the bilayer, to the third, fifth, and possibly sixth transmembrane loops. The β receptor acts through a guanine nucleotide-binding protein, or G protein, which links the receptor functionally with the effector enzyme, adenylyl cyclase. Adenylyl cyclase in turn produces cyclic adenosine monophosphate, which is the "second messenger" considered to be responsible for the activity of β agonists, such as bronchodilation.

Development of β Agonist Bronchodilators

The prototypical drug in the adrenergic bronchodilator group is epinephrine, a naturally-occurring, endogenous sympathetic neurotransmitter. Adrenergic bronchodilators, and the later agents, which were β-2-specific agonists, represent modifications of the chemical compound, β phenylethylamine, illustrated in Figure 2.

The aromatic portion consists of the benzene (or phenyl) ring together with the aliphatic ethylamine side chain. The terminal amine and the benzene ring are connected by an α and β carbon, which should not be confused with the α and β receptors of the sympathetic nervous system.

β Agonists as Stereoisomers

Molecular compounds with carbon atoms that are bonded to 4 different atoms or groups can have two distinct spatial arrangements that give them an asymmetry, or chirality. An example is given by the β carbon on the ethylamine side chain of the adrenergic drug molecules. Rotation about this chiral, or asymmetric center, produces two nonsuperimposable mirror images, termed enantiomers, or simply isomers, as shown in Figure 3 for β-phenylethylamine with an OH group on the β carbon.

Enantiomers have similar physical and chemical properties (melting points, boiling points, solubility, chemical reactivity).[15] However, they do not have the same receptor specificity and therefore do not have the same physiologic effects. The two mirror images of the β OH phenylethylamine analogues rotate light in opposite directions, leading to their designation as dextrorotatory (*D*) or levorotatory (*L*). Based on absolute spatial configuration, these isomers are referred to as R- (levo-) or S- (dextro-), respectively. The R- (levo-) form of epinephrine is active on the β receptor and produces bronchodilation. β agonists have been produced synthetically as racemic mixtures (ie, a 50:50, equimolar mix of the R- and S-isomers). Natural epinephrine, such as that obtained from bovine extract, occurs as the R- (levo-) isomer only, whereas the inhaled aerosol formulation is the racemic mixture. A newly released (March 1999) drug, levalbuterol, is the single R-isomer form of racemic albuterol.

Specific Adrenergic Bronchodilators

The development of drugs in the β agonist bronchodilator group has followed from modifications to the original

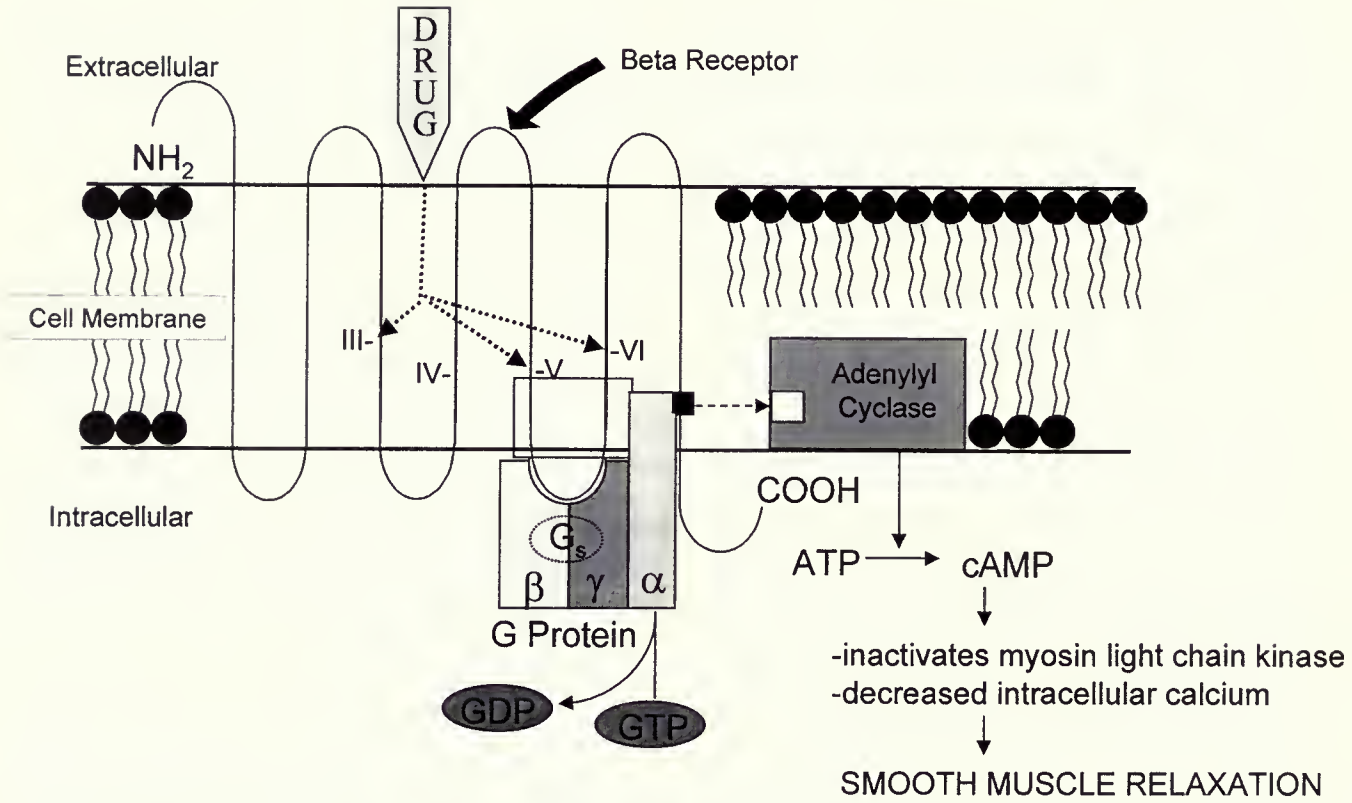
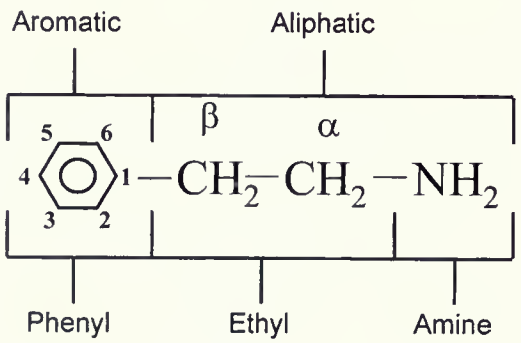


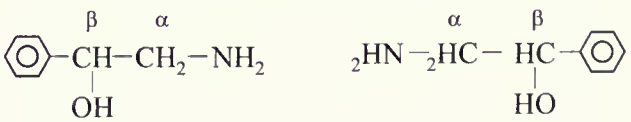
Fig. 1. A simplified two-dimensional view of the β receptor, which is a polypeptide traversing the cell lipid membrane 7 times, with an extracellular and an intracellular terminus, and which is linked to a guanine-binding protein on the intracellular face. GDP = guanosine 5′-diphosphate. GTP = guanosine 5′-triphosphate. ATP = adenosine 5′-triphosphate. cAMP = cyclic adenosine monophosphate.



β– phenylethylamine

Fig. 2. The parent compound of the adrenergic bronchodilator drugs, β phenylethylamine. (Modified from Reference 3, with permission.)

β–OH phenylethylamine



l- or R-isomer *d*- or S-isomer

Fig. 3. The R- and S-isomers of β phenylethylamine, showing the hydroxyl group on the β carbon. The two isomers are mirror images, or enantiomers, designated as levorotatory (L) or R-, and dextrorotatory (D) or S-. (From Reference 3, with permission.)

chemical structure of epinephrine, with changes in both the catechol nucleus and the amine side chain, as seen in Figure 4. Specificity for the β-2 receptor was explained by the "keyhole" theory of β adrenergic receptors, which stated that the larger the moiety attached to the nitrogen end of the catecholamine, the greater the β-2 specificity.[9,16] In general, longer duration of action was obtained by modifying the catechol ring, and greater β-2 specificity was seen with enlargement of the moiety attached to the amine group. More recent modifications of the length of the ethylamine side chain led to long-acting compounds such as salmeterol. The most recent development has been isolation of the single isomer molecule to replace the racemic mixture, as illustrated by levalbuterol. Table 1 lists the adrenergic bronchodilator group used as orally inhaled agents, and includes the older drugs, isoproterenol and isoetharine, for completeness and comparison.

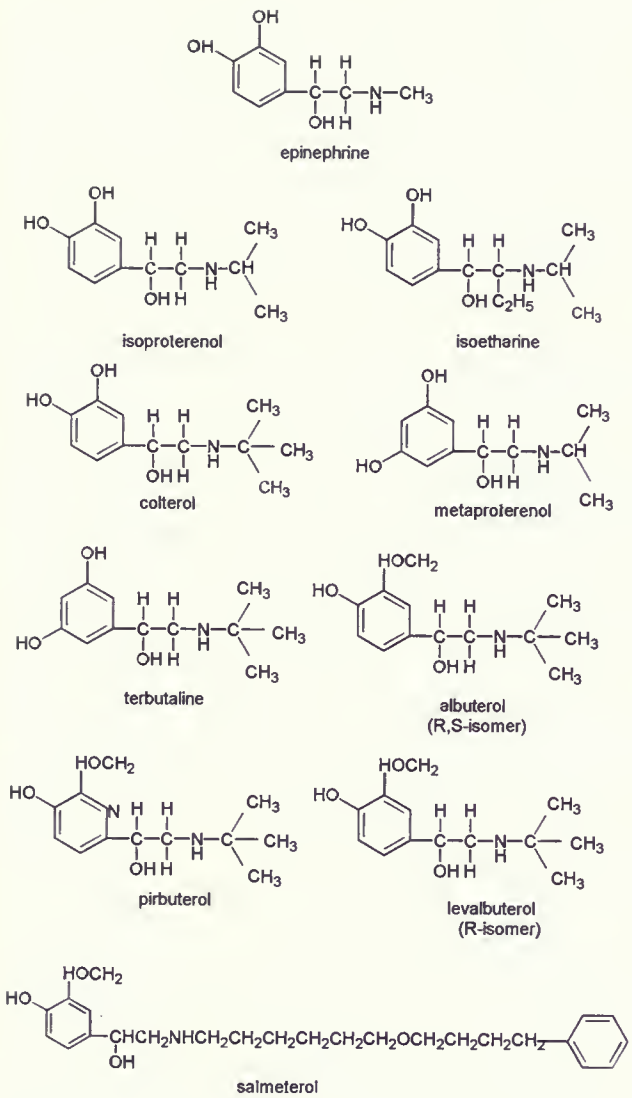


Fig. 4. Structures of epinephrine and other adrenergic bronchodilators available as orally inhaled aerosol formulations. With the exception of natural epinephrine and levalbuterol, all formulations are racemic mixtures and are shown in the same orientation for clarity. The isomers of racemic albuterol and levalbuterol are labeled to indicate the difference in these two drugs.

Epinephrine (adrenaline). Epinephrine is referred to as a catecholamine, since the benzene ring with its hydroxyl attachments forms a catechol nucleus, to which is attached the amine side chain. A catecholamine such as epinephrine, isoproterenol, or isoetharine is rapidly metabolized by the enzyme, catechol-O-methyl-transferase, or COMT. The enzyme methylates the carbon-3 hydroxyl attachment on the catechol nucleus, thereby inactivating the drug. Epinephrine stimulates both α and β adrenergic receptors. It has the smallest moiety attached to the terminal nitrogen of all the inhaled adrenergic bronchodilators, resulting in no β-2 specificity. Because of its lack of receptor specificity, there is a high prevalence of adverse effects, such as tachycardia, elevated blood pressure, tremor, headache, and insomnia, in addition to the desired therapeutic effect of bronchodilation. The bronchodilatory effect of epinephrine is very rapid in onset, but also quite short, approximately one hour of duration, since the drug is metabolized by COMT and monoamine oxidase.

As previously stated, the inhaled formulation of epinephrine is the racemic mixture of the naturally-occurring R-isomer. Since only the R-isomer is active on the adrenergic receptors, a 1:100 strength formulation of the natural, single-isomer form is used for inhalation, whereas the racemic mixture is a 2.25% strength solution. Since epinephrine is active on α adrenergic receptors as well as β receptors, it is often used as a topical vasoconstrictor in treating stridor and croup, and during endoscopy to control bleeding.[3,17]

Isoproterenol (isoprenaline). Isoproterenol has an isopropyl group attached to the terminal nitrogen, giving it a larger group at this site and, in keeping with the keyhole theory of β-2 specificity, shifts its activity from α to largely β stimulation. Since the catechol nucleus remains the same as epinephrine, the drug is still vulnerable to inactivation by COMT, giving it a very short duration, approximately 1.5–2 hours. Since isoproterenol is a potent but nonspecific β agonist, activating both β-1 and β-2 receptors, tachycardia is a common adverse effect, even when administered via inhalation. Isoproterenol lacks the pressor effects of epinephrine and can cause vasodilation in sufficient parenteral doses. A combination of isoproterenol 0.25% and cyclopentamine 0.5% (an α receptor agonist) was marketed in the 1970s as Aerolone, in a dose of 0.5 mL for nebulizer treatment. The combined α and β effects with the compound were thought to produce bronchodilation with vasoconstriction (decongestion) in the airway, similar to the broader effects seen with epinephrine.[18]

Isoetharine. Isoetharine has an ethyl group attached to the α carbon atom of the amine side chain, in addition to the isopropyl group at the terminal nitrogen seen with isoproterenol. This further increase in side chain bulk made isoetharine the first β-2-specific inhaled aerosol bronchodilator, which was available in a metered-dose form (Bronkometer) and a 1% nebulizer solution (Bronkosol). Although its bronchodilator activity is less than isoproterenol, the minimal cardiac adverse effects made it a more attractive β agonist for many clinicians in the 1970s in the United States.[9] Since it is also a catecholamine, the duration of action was limited to approximately 1.5–2 hours. An original formulation of isoetharine (Bronkosol) contained phenylephrine, a pure α agonist as well as thenyldiamine, an antihistamine. Both phenylephrine and thenyldiamine were subsequently deleted from the formulation.

Table 1. Inhaled Adrenergic Bronchodilator Agents Currently Available in the United States

Drug	Brand Name	Receptor Preference	Adult Dosage	Time Course (onset, peak, duration)
epinephrine	Adrenalin	(α, β)	SVN: 1% solution, 0.25–0.5 mL (2.5–5.0 mg), qid MDI: 0.2 mg/puff, 2 puffs, as ordered or needed	3–5 min 5–20 min 1–3 h
racemic epinephrine	microNefrin	(α, β)	SVN: 2.25% solution, 0.25–0.5 mL (5.63–11.25 mg), qid	3–5 min 5–20 min 0.5–2 h
isoproterenol	Isuprel	(β)	SVN: 0.5% solution, 0.25–0.5 mL (1.25–2.5 mg), qid MDI: 131 μg/puff, 2 puffs, qid	2–5 min 5–30 min 0.5–2 h
isoetharine	Bronkosol	(β-2)	SVN: 1% solution, 0.25–0.5 mL (2.5–5.0 mg), qid MDI: 340 μg/puff, 1–2 puffs, qid	1–6 min 15–60 min 1–3 h
terbutaline	Brethine	(β-2)	MDI: 200 μg/puff, 2 puffs, q 4–6 h	5–30 min 30–60 min 3–6 h
metaproterenol	Alupent	(β-2)	SVN: 5% solution, 0.3 mL (15 mg), tid, qid MDI: 650 μg/puff, 2–3 puffs, tid, qid	1–5 min 60 min 2–6 h
albuterol	Proventil Proventil HFA Ventolin	(β-2)	SVN: 0.5% solution, 0.5 mL (2.5 mg), tid, qid MDI: 90 μg/puff, 2 puffs, tid, qid DPI: 200 μg capsule, 1 capsule, q 4–6 h	15 min 30–60 min 5–8 h
bitolterol	Tornalate	(β-2)	SVN: 0.2% solution, 1.25 mL (2.5 mg), bid-qid MDI: 370 μg/puff, 2 puffs, q 8 h	3–4 min 30–60 min 5–8 h
pirbuterol	Maxair	(β-2)	MDI: 200 μg/puff, 2 puffs, q 4–6 h	5 min 30 min 5 h
salmeterol	Serevent	(β-2)	MDI: 21 μg/puff, 2 puffs, bid DPI: 50 μg/blister, 1 inhalation bid	20 min 3–5 h 12 h
levalbuterol	Xopenex	(β-2)	SVN: 0.63 mg, q 6–8 h or 1.25 mg, tid	15 min 30–60 min 5–8 h

SVN = small-volume nebulizer. MDI = metered-dose inhaler. DPI = dry powder inhaler.

Bitolterol. Although bitolterol was not the next inhaled β agonist to become available after isoetharine in the United States, it can be considered with the other catecholamines such as epinephrine, isoproterenol, and isoetharine. Bitolterol to date has been the only prodrug approved for use as an inhaled bronchodilator in the United States. The prodrug form, bitolterol, possesses two toluate ester groups on the benzene ring at the carbon 3 and 4 positions. Esterase enzymes present in the lung hydrolyze bitolterol to the active catecholamine form, colterol. The hydrolysis proceeds gradually, giving bitolterol a longer duration of action, possibly 5–8 hours, and the bulky side chain confers β-2 specificity. Although interesting from a pharmacological perspective, bitolterol was not widely accepted for clinical use.

Metaproterenol (orciprenaline). Metaproterenol introduced a new generation of β agonists by modifying the catechol ring structure to produce a resorcinol. The hydroxyl groups were shifted from the carbon 3 and 4 positions to the "meta" position of carbons 3 and 5. This prevented degradation by COMT, allowing longer duration of action, 4–6 hours. Except for the change in the catechol attachments, metaproterenol is the same as isoproterenol, and has substantial cardiac adverse effects, compared to subsequent β-2-specific agonists.

Terbutaline. Terbutaline became available for parenteral (subcutaneous) use in the 1970s, and later was released in a metered-dose inhaler (MDI) formulation. Terbutaline possesses a tertiary butyl group on the terminal nitrogen of the side chain, giving it greater β-2 specificity than isoetharine or metaproterenol. The drug has the same 3,5 meta-dihydroxy groups as metaproterenol, making it a member of the resorcinol group and thereby increasing its duration of action to 4–6 hours. Because the MDI formulation was not available originally, and terbutaline was considered by many clinicians to be superior to metaproterenol, the injectable ampule solution of 1 mg/mL was often used as a nebulizer solution. Dosing was largely empirical and, based on personal knowledge, could range from 0.5 mg to as much as 9 or 10 mg in a nebulizer treatment.

Albuterol (Salbutamol). Albuterol is identical chemically to terbutaline, with the exception of a methanol attachment at the carbon 3 position of the benzene ring, making it a saligenin. The drug possesses β-2 specificity as well as an approximately 6-hour duration of action because of its protected ring structure and bulky side chain. Albuterol is available in multiple dosing forms, including a nebulizer solution, an MDI, a dry powder inhaler, and oral tablets. An extended release oral tablet formulation is also available. Because of its versatile formulations, good bronchodilating action, and minimal adverse effects, albuterol became the most commonly prescribed bronchodilator in reactive airways disease in the United States during the 1980s and 1990s.

Pirbuterol. Pirbuterol is structurally identical to albuterol, with one exception: a nitrogen atom is inserted in place of the second carbon atom on the benzene ring, forming a pyridine nucleus. Pirbuterol is also β-2 specific and has an approximately 5-hour duration of bronchodilating action. This drug has been available in the United States in either a pressurized MDI or a breath-actuated MDI (Autohaler) to minimize hand-breath coordination problems.[19]

Salmeterol. Although a sustained-release formulation of albuterol intended to provide extended bronchodilation for up to 12 hours had been previously released, salmeterol, approved in 1994, represents the first true long-acting β agonist bronchodilator in the inhaled aerosol group. Salmeterol xinafoate is the 1-hydroxy-2-naphthoic salt of salmeterol base, with 36.25 μg of the salt equivalent to 25 μg of the base. The drug is a modification of albuterol, with a long lipophilic N-substituted side chain. The long side chain increases the lipophilicity of salmeterol and binds to an area of the β receptor within the lipid membrane referred to as an exosite. With the lipophilic tail anchored, the active phenyl ethanolamine "head" alternately engages and disengages from the active receptor site, thus providing ongoing stimulation of the receptor and giving a 12-hour duration of action. The drug is ultimately metabolized by hydroxylation, with elimination in the feces.[20,21]

Levalbuterol. In March of 1999 the single R-isomer form of racemic albuterol, levalbuterol, was approved for general clinical use in the United States as Xopenex, in a 0.63 mg and 1.25 mg unit dose for nebulization. With the exception of natural epinephrine, which is the R- (*L*) isomer, levalbuterol is the only single-isomer β agonist available at this time. The 0.63 mg dose is comparable to the 2.5 mg racemic albuterol dose in onset and duration, and the 1.25 mg dose has shown a higher peak effect on flow, with an 8-hour duration in a study by Nelson et al.[22]

Adverse Effects With β Agonists

General Adverse Effects

The development of the β agonist drug class has been toward increasing receptor selectivity with minimal adverse effects. Table 2 lists adverse effects that can be seen with β agonists and that are dose-dependent. With newer β-2-selective agents, the most common adverse effect in standard doses is tremor, with shakiness, irritability, insomnia, and headache also reported. These effects are typical adrenaline-mediated responses seen with sympathetic nervous system activation. Older catecholamine agents that lacked β-2 specificity increased cardiac output and oxygen consumption. The β-2-selective agents can also stimulate tachycardia in sufficient doses, but agents such as terbutaline or albuterol can improve cardiac performance with reduced afterload through peripheral vasodilation.[23] Clinically important hyperglycemia and hypokalemia are not commonly seen in standard doses, but can become important in a dose-dependent fashion with high doses or continual nebulization.[24,25] A drop in arterial partial pressure of oxygen is possible, with mismatched ventilation/perfusion during reversal of bronchoconstriction, but has not been found to be clinically important, and is transient. This

Table 2. Possible Adverse Effects of Beta Agonists

Tremor
Palpitations, tachycardia
Increased blood pressure
Headache
Insomnia
Nervousness
Dizziness
Nausea
Tolerance
Decrease in P_{aO_2}
Hypokalemia
Hyperglycemia
FREON-induced bronchospasm (MDIs only)

P_{aO_2} = arterial partial pressure of oxygen.
MDI = metered-dose inhaler.

was noted with isoproterenol in asthma patients, but the decrease in arterial partial pressure of oxygen was ≤ 15 mm Hg, and reversed within 15–20 minutes.[25]

Tolerance to β Agonists

Of more concern is the tachyphylaxis and tolerance that may occur with exposure to β agonists. The development of tolerance to β agonist bronchodilators is a complex phenomenon. The terms tachyphylaxis and tolerance actually describe a multiple-stage process of changes in the β receptor with agonist exposure.

Initial exposure to a β agonist produces a rapid desensitization of the β-2 receptor through a process of uncoupling of the receptor from the enzyme effector system.[13,14] This is a transient process and is quickly reversed with removal of the agonist, to allow further receptor stimulation. With more prolonged exposure to a β agonist, there is some loss of cell surface receptors through a process described as internalization or sequestration.[13] This internalization may be part of the sequence of resensitization of the receptor through dephosphorylation. Internalization may require hours for reversal. With hours of agonist exposure there is a net loss of cellular receptors, termed down-regulation. This is denoted as long-term desensitization.[14] These desensitization processes regulate a certain refractory state of the β receptor itself. In addition, β agonists can negatively modulate β-2 receptor gene expression, leading to longer-term down-regulation and loss of β receptors. Hayes et al reported a 22% decrease in β receptor density in the lung, measured via positron emission tomography scanning, with albuterol 4 mg orally bid and 200 μg inhaled qid over two weeks, with a reduction in bronchodilator response.[26]

These processes result clinically in (1) some decline in bronchodilator response following continual maintenance treatment with a β agonist, (2) decline in adverse effects such as tachycardia and muscle tremor, and (3) loss of bronchoprotection against airway challenge.

Corticosteroids can increase β-2 receptor gene transcription, leading to up-regulation of the receptors.[14] This effect further supports the use of corticosteroids in asthma, both for preserving β receptor density and for their anti-inflammatory effects.

The "Asthma Paradox"

Despite improvements in receptor-specific β agonist bronchodilators, there have been troubling associations between increased deaths from asthma and the use of these agents, a situation that has been termed the "asthma paradox."[27]

Asthma Mortality. In the 1960s, there was a reported increase in deaths among asthma patients in Great Britain, where a high-dose formulation of isoproterenol (known as isoprenaline-forte) with 400 μg per puff was used.[28,29] The asthma death rate returned to previous levels following removal of the product from the market.[30] Data from New Zealand in the 1980s showed another increase in asthma mortality and suggested an association with inhaled fenoterol (200 μg/puff), a potent β agonist.[31] Interpretation of the New Zealand data has been questioned by others, who found no correlation between asthma mortality in that country and use of the inhaled β agonists, fenoterol, and albuterol.[32] It has been noted that asthma mortality subsequently declined in New Zealand, despite increasing sales of all β agonists, including fenoterol.[33] In 1992, Spitzer et al published results from a Canadian case-control study that found an association between asthma mortality and the use of β agonist bronchodilators.[34] The use of two or more canisters per month of fenoterol or albuterol was associated with an increased risk of death. Obviously, the question becomes: is increased use of a β agonist a marker of asthma severity, or causal in nature? A correlational study can only indicate an association, not causality.

Asthma Morbidity. It has been suggested that not only mortality but asthma morbidity may be negatively affected by β agonist use. A study by Sears et al published in 1990 concluded that intermittent use of a β agonist (fenoterol) gave better asthma control than regular treatment, based on results with 64 mildly-to-moderately asthmatic subjects.[35] Control was evaluated using morning and evening peak flows, symptom diaries, use of rescue β agonist, and need for oral prednisone. In 17 subjects asthma was better controlled with regular inhaled bronchodilator, whereas in 40 subjects control was superior with as-needed bronchodilator use. Seven subjects showed no difference between the two treatment regimens. Mean values and magnitude

of change in the measures used were not reported originally, only the percentage of patients showing a change, and this has been pointed out as a limitation of the report.[30] A subsequent report provided lung function data from the study of Sears et al, showing an approximately 5% difference in forced expiratory volume in the first second between regular use and rescue use of inhaled fenoterol.[36]

Loss of Bronchoprotection. There have also been data to indicate that there is a heightened sensitivity to bronchoconstricting stimuli with β agonist use, although bronchodilator effects remain. The loss of bronchoprotection has raised concerns that β agonists may actually "sensitize" asthmatics to inflammatory stimuli. O'Connor et al examined the protective effect of a single 500 μg inhalation of terbutaline with adenosine monophosphate and methacholine challenge, before and after 7 days of treatment with 500 μg of terbutaline qid. There was a significant decline in the PC_{20} (provocational concentration [ie, dose] producing a 20% decrease in forced expiratory volume in the first second) for both adenosine monophosphate and methacholine after 7 days of treatment.[37] Cockcroft et al found a greater loss of protection against allergen than against methacholine in mildly asthmatic subjects treated for 14 days with albuterol 200 μg qid.[38] The implication of these effects is that, with regular β agonist treatment, asthmatics may show a bronchodilator response that masks increased sensitivity to airway allergens.

Is the S-isomer Inactive?

It has been accepted in the past that only one of the stereoisomers of epinephrine analogues is physiologically active. Recent in vitro and clinical data[39–43] suggest that the S-isomer form of albuterol may have effects that can antagonize the desired bronchodilating action of the R-isomer. Table 3 summarizes the physiologic effects of the S-isomer of albuterol. Templeton et al found that (S)-salbutamol ([S]-albuterol) enhanced the contractile response of isolated human bronchial tissue to stimuli by histamine and leukotriene C_4.[39]

Mitra et al showed that S-albuterol increases intracellular free calcium in bovine tracheal smooth muscle cells.[40] In contrast, R-albuterol decreased calcium concentrations in the same study. More interesting was the finding that the increase in calcium from S-albuterol was blocked by atropine, implying that the S-isomer attaches to muscarinic receptors and not β receptors. Work by Volcheck et al found that the S-isomer of albuterol significantly enhanced superoxide production by eosinophils in response to interleukin 5 stimulus in vitro, whereas racemic mixtures containing both the R- and S-isomers inhibited such production.[41] Superoxide production is a marker of inflammatory activity, and this finding implies that the S-isomer of albuterol has a pro-inflammatory effect. A difference in the rate of metabolism of the two isomeric forms of albuterol has also been found. Boulton et al found higher plasma levels of the S-isomer than the R-isomer with oral dosing of racemic albuterol in 12 healthy males.[42] The accumulation of the S-isomer could further contribute to possible pro-inflammatory effects with the administration of a racemic mixture of albuterol. Dhand et al recently reported lower plasma levels of (S)-albuterol than (R)-albuterol when racemic albuterol was administered via MDI or MDI with holding chamber.[44] They attributed this interesting finding to a preferential retention of the S-isomer in the lung when inhaled. This result contrasts with plasma levels of (R)- and (S)-albuterol when given via nebulization or dry powder inhaler.[45,46]

Table 3. Summary of the Physiological Effects of (S)-Albuterol

Effect	Reference
Increases intracellular calcium concentration	Mitra, 1993[40]
Binds to muscarinic receptors	Mitra, 1993[40]
Enhances experimental airway responsiveness	Johansson, 1996[43]
Increases contractile response of bronchial tissue to histamine or leukotriene C_4 (LTC_4)	Templeton, 1998[39]
Enhances eosinophil superoxide production with interleukin-5 stimulation	Volcheck, 1998[41]
Slower metabolism than R-albuterol, with accumulating plasma levels*	Boulton, 1997[42]

*Finding may vary with metered-dose inhaler or metered-dose inhaler with holding chamber aerosol administration.[44]

β Agonists and the National Asthma Education and Prevention Program Guidelines

Discussion of a possible relationship between β agonists and asthma should occur in the context of the recently revised National Asthma Education and Prevention Program guidelines for asthma treatment and prevention. Both the 1991 and the 1997 document clearly differentiate β agonists (with the exception of salmeterol) as "relievers" and not "controllers."[47] This distinction aligns with the increased emphasis on asthma as a disease of chronic airway inflammation. Treatment of bronchospasm with a β agonist addresses symptoms and effects of the inflammation, but not the underlying inflammation process itself. Such a view of asthma would predict that rescue treatment will ultimately be unsatisfactory as primary or sole therapy. This shift in understanding of the pathophysiology of asthma changes our understanding of the use of β agonists in managing asthma. Anti-inflammatory agents become

the drug of choice to manage persistent asthma. This may reduce the association seen between β agonists and asthma mortality.

The exact effect of β agonists in asthma remains a subject of debate. Several hypotheses can be advanced to explain the apparent worsening of asthma with use of β agonists:

- β agonists cause increased sensitivity to allergenic and irritant stimuli in asthmatics, possibly through down-regulation of β receptors in the airway.
- β agonists may be used by practitioners to manage asthma with inadequate or no anti-inflammatory therapy.
- Self-reliance on rescue β agonist therapy when confronted with worsening airway obstruction is substituted for professional medical treatment, with potentially lethal delays in seeking treatment.
- Accumulation of the S-isomer of racemic β agonist mixtures exerts deleterious or pro-inflammatory effects in the airway.
- There is increased airway irritation (as well as increasing asthma prevalence) with increased environmental pollutants and with lifestyle changes that cause increased allergen exposure.

Ultimately, the changes seen in the prevalence of asthma may reflect multiple factors and the interaction of these factors rather than a single cause.

Summary

The adrenergic bronchodilators that have been developed for oral inhalation represent successive refinement in terms of receptor specificity and duration of action. β agonist bronchodilators have durations of 4–6 hours, or, in the case of salmeterol, of up to 12 hours, offering convenient dosing. Inhalation of the aerosol formulations targets the lung directly. The release of levalbuterol now provides an agent with a single isomer active on β-2 receptors. The currently available agents offer clinicians and patients with reversible obstructive lung disease a choice of sophisticated drugs for airway smooth muscle relaxation. Although improvements in the drugs have reduced adverse effects and β agonists are considered safe, concerns persist about the effect of β agonists in asthma. An improved understanding of asthma pathophysiology may lead to more appropriate use of β agonists in asthma.

REFERENCES

1. Chen KK, Schmidt CF. The action of ephedrine, the active principle of the Chinese drug Ma Huang. J Pharmacol Exp Ther 1925;24:339.
2. Solis-Cohen S. The use of adrenal substance in the treatment of asthma. JAMA 1900;34:1164.
3. Aranson R, Rau JL. The evolution of beta-agonists. Respir Care Clin N Am 1999;5(4):479–519.
4. Hartung WH. Epinephrine and related compounds: influence of structure on physiologic activity. Chem Rev 1931;9:389.
5. Wilson NL. Clinical notes on adrenalin. Laryngoscope 1901;Jul:63–66.
6. Bullowa JGM, Kaplan DM. On the hyperdermatic use of adrenalin chloride in the treatment of asthmatic attacks. Med News 1903;83: 787.
7. Kahn R. Zur physiologie der trachea. Arch Physiol 1907;398–426.
8. Barger G, Dale HH. Chemical structure and sympathomimetic action of amines. J Physiol 1910;41:19.
9. Leifer KN, Wittig HJ. The beta-2 sympathomimetic aerosols in the treatment of asthma. Ann Allergy 1975;35(2):69–80.
10. Ahlquist RP. A study of the adrenotropic receptors. Am J Physiol 1948;153:586–600.
11. Lands AM, Arnold A, McAuliff JP, Luduena FP, Brown TG Jr. Differentiation of receptor systems activated by sympathomimetic amines. Nature (London) 1967;214:597–598.
12. Fraser CM, Venter JC. Beta-adrenergic receptors: Relationship of primary structure, receptor function, and regulation. Am Rev Respir Dis 1990;141(2 Pt 2):S22–S30.
13. Johnson M. The β-adrenoceptor. Am J Respir Crit Care Med 1998; 158(5 Pt 3):S146–S153.
14. Jenne JW. $Beta_2$-adrenergic receptor-agonist interaction. In: Leff AR, editor. Pulmonary and critical care pharmacology and therapeutics. New York: McGraw-Hill; 1996: 451–462.
15. Bakale RP, Wald SA, Butler HT, Gao Y, Hong Y, Nie X, Zepp CM. Albuterol: a pharmaceutical chemistry review of R-, S-, and RS-albuterol. Clin Rev Allergy Immunol 1996;14(1):7–35.
16. Brittain RT, Jack D, Ritchie AC. Recent β-adrenoceptor stimulants. Adv Drug Res 1970;5:197-253.
17. Dickison AE. Child with upper airway obstruction: Part III. Respir Management 1990;20:66.
18. Rau JL. Respiratory therapy pharmacology (1/e). Chicago: Year Book; 1978.
19. Richards DM, Brogden RN. Pirbuterol: a preliminary review of its pharmacological properties and therapeutic efficacy in reversible bronchospastic disease (review). Drugs 1985;30(1):6–21.
20. Brogden RN, Faulds D. Salmeterol xinafoate: a review of its pharmacological properties and therapuetic potential in reversible obstructive airways disease. Drug Eval 1991;42(5):895.
21. Dahl R, Earnshaw JS, Palmer JBD. Salmeterol: a four week study of a long-acting beta-adrenoceptor agonist for the treatment of reversible airways disease. Eur Respir Dis 1991;4(10):1178–1184.
22. Nelson HS, Bensch G, Pleskow WW, DiSantostefano R, DeGraw S, Reasner DS, Rollins TE, Rubin PD. Improved bronchodilation with levalbuterol compared with racemic albuterol in patients with asthma. J Allergy Clin Immunol 1998;102(6 Pt 1):943–952.
23. McFadden ER Jr. Clinical use of β-adrenergic agonists. J Allergy Clin Immunol 1985;76(2 Pt 2):352-356.
24. Shrestha M, Bidadi K, Gourlay S, Hayes J. Continuous vs intermittent albuterol at high and low doses, in the treatment of severe acute asthma in adults. Chest 1996;110(1):42–47.
25. Jenne JW. Physiologic actions of beta-adrenergic agonists. In: Leff AR, editor. Pulmonary and critical care pharmacology and therapeutics. New York: McGraw-Hill; 1996: 473–482.
26. Hayes MJ, Qing F, Rhodes CG, Rahman SU, Ind PW, Sriskandan S, et al. In vivo quantification of human pulmonary β-adrenoceptors: effect of β-agonist therapy. Am J Respir Crit Care Med 1996;154(5): 1277–1283.
27. Page CP. Beta agonists and the asthma paradox. J Asthma 1993; 30(3):155–164.
28. Speizer FE, Djoll R, Heaf P, Strang LB. Investigation into use of drugs preceding death from asthma. Br Med J 1968;(5588):339-343.

29. Stolley P. Asthma mortality: why the United States was spared an epidemic of deaths due to asthma. Am Rev Respir Dis 1972;105(6): 883–890.
30. McFadden ER Jr. The β_2-agonist controversy revisited. Ann Allergy Asthma Immunol 1995;75(2):173–176.
31. Granger J, Woodman K, Pearce N, Crane J, Burgess C, Keane A, et al. Prescribed fenoterol and death from asthma in New Zealand, 1981–1987: a further case-control study. Thorax 1991;46(2):105–111.
32. Haas JF, Staudinger HW, Schuijt C. Asthma deaths in New Zealand. Br Med J 1992;304(6482):1634.
33. Crane J, Buragess C, Pearce N, Beasley R, Jackson R. Asthma deaths in New Zealand. Br Med J 1992;304(6837):1307.
34. Spitzer WO, Suissa S, Ernst P, et al. The use of β-agonists and the risk of death and near death from asthma. N Engl J Med 1992; 326(8):501–506.
35. Sears MR, Taylor DR. Print CG, Lake DC, Li QQ, Flannery EM, et al. Regular inhaled beta-agonist treatment in bronchial asthma. Lancet 1990;336(8728):1391–1396.
36. Taylor DR, Sears MR, Herbison GP, Flannery EM, Print CG, Lake DC, et al. Regular inhaled β-agonist in asthma: effects on exacerbations and lung function. Thorax 1993;48(2):134–138.
37. O'Connor BJ, Aikman S, Barnes PJ. Tolerance to the nonbronchodilator effects of inhaled β_2-agonists in asthma. N Engl J Med 1992; 327(17):1204–1208.
38. Cockcroft DW, McParland CP, Britto SA, Swystun VA, Rutherford BC. Regular inhaled salbutamol and airway responsiveness to allergen. Lancet 1993;342(8875):833–837.
39. Templeton AGB, Chapman ID, Chilvers ER, Morley J, Handley DA. Effects of S-salbutamol on human isolated bronchus. Pulm Pharmacol Therapeutics 1998;11(1):1–6.
40. Mitra S, Ugur M, Ugur O, Goodman HM, McCullough JR, Yamaguchi H. (S)-albuterol increases intracellular free calcium by muscarinic receptor activation and a phosphoplipase C-dependent mechanism in airway smooth muscle. Molec Pharmacol 1998;53(3):347–354.
41. Volcheck GW, Gleich GJ, Kita H. Pro- and anti-inflammatory effects of beta adrenergic agonists on eosinophil response to IL-5. J Allergy Clin Immunol 1998;101:S35.
42. Boulton DW, Fawcett JP. Pharmcokinetics and pharmacodynamics of single oral doses of albuterol and its enantiomers in humans. Clin Pharmacol Ther 1997;62(2):138–144.
43. Johansson F, Rydberg I, Aberg G, Andersson RG. Effects of albuterol enantiomers on in vitro bronchial reactivity. Clin Rev Allergy Immunol 1996;14(1):57–64.
44. Dhand R, Goode M, Reid R, Fink JB, Fahey PJ, Tobin MJ. Preferential pulmonary retention of (S)-albuterol after inhalation of racemic albuterol. Am J Respir Crit Care Med 1999;160(4):1136–1141.
45. Lipworth BJ, Clark DJ, Koch P, Arbeeny C. Pharmacokinetics and extrapulmonary β_2 adrenoceptor activity of nebulised racemic salbutamol and its R and S isomers in healthy volunteers. Thorax 1997; 52(10):849–852.
46. Schmekel B, Rydberg I, Norlander B, Sjöswärd KN, Ahlner J, Adnersson RG. Stereoselective pharmacokinetics of S-salbutamol after administration of the racemate in healthy volunteers. Eur Respir J 1999;13(6):1230–1235.
47. National Asthma Education and Prevention Program. Expert Panel Report 2: Guidelines for the diagnosis and management of asthma. Bethesda, 1997; National Institutes of Health, NHLBI, NIH Publication No. 97–4051. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm. Accessed June 6, 2000.

Clinical Aspects of Inhaled Anticholinergic Therapy

Sammy C Campbell MD

Introduction
Muscarinic Receptors
Antimuscarinic Drug Effects in the Lung
Use of Antimuscarinic Therapy in Obstructive Airway Disease
Current Antimuscarinic Therapy
Combination Therapy
New Antimuscarinic Drugs
Summary [Respir Care 2000;45(7):864–867] *Key words: lung disease, obstructive, bronchodilator, ipratropium, tiotropium, muscarinic, anticholinergic.*

Introduction

The term "anticholinergic" refers to a pharmacologic action that opposes cholinergic receptor stimulation. In the lung, the cholinergic receptors that cause airways obstruction are of the muscarinic type. Atropine is the most commonly used antimuscarinic drug, and ipratropium is the most commonly used inhaled antimuscarinic drug. These two drugs represent two types of muscarinic antagonists, those that have a tertiary amine and those that have a quaternary amine as part of their formulas (Table 1). The tertiary drugs include atropine sulfate and atropine phosphate. These drugs penetrate easily into body tissue and cause more cardiac and central nervous system adverse effects than the quaternary drugs. The quaternary drugs are safer because they do not easily cross into the brain (or across the placenta). Atropine methonitrate, flutropium bromide, glycopyrrolate, and ipratropium bromide are quaternary medications, and are administered via inhalation to treat lung disease, although tertiary drugs may also be used. In general, quaternary drugs require half the dose of a similar tertiary drug to produce the same amount of bronchodilation. Hence, 500 μg of ipratropium or glycopyrrolate produces the same bronchodilation as 1 mg of atropine.

Muscarinic Receptors

There are 5 types of muscarinic receptors, designated M1 to M5.[1,2] M1, M2, and M3 receptors are stimulated by acetylcholine and are found at various sites within the lung (Table 2). The M1 receptors in the parasympathetic ganglia facilitate transmission of the nerve impulse. At the site of innervation, the M3 receptor causes the parasympathetic effect, and the M2 receptor works as a feedback inhibitor to prevent more acetylcholine release at this site. The parasympathetic ganglia containing the M1 receptors are located on the airways. Activation of the M1 receptor facilitates transmission of the neural impulse to the nerve that goes to the mucous gland, airway smooth muscle, or perhaps other sites within the lung. The M1 receptors within the ganglia are inhibited by β sympathomimetic receptors. Blockade of these β receptors by β blocker drugs can cause unopposed muscarinic activity to the airways, resulting in bronchospasm. This is why an antimuscarinic agent such as atropine or ipratropium is the most effective therapy for bronchospasm resulting from use of a β blocking drug. There are M1 receptors within other lung sites. Some studies indicate that antagonism of these receptors may result in bronchodilation. The M3 receptor is understood to be the main receptor blocked by antimuscarinic therapy, resulting in bronchodilation. The M3 receptor is at the site of muscle and mucous gland innervation. This

Sammy C Campbell MD is affiliated with the University of Arizona College of Medicine, Pulmonary Section, Veterans Affairs Medical Center of Southern Arizona, Tucson, Arizona.

A version of this paper was presented by Dr Campbell during the New Horizons Symposium, "Clinical Pharmacology of Inhaled Agents for the Respiratory Care Clinician," at the American Association for Respiratory Care's 45th International Respiratory Congress, December 14, 1999, in Las Vegas, Nevada.

Correspondence: Sammy C Campbell MD, University of Arizona College of Medicine, Pulmonary Section, Veterans Affairs Medical Center of Southern Arizona, 3601 South 6th Avenue, Tucson AZ 85723. E-mail: Sammy.Campbell@med.va.gov.

Table 1. Tertiary and Quaternary Muscarinic Antagonists Used As Inhaled Therapy for Lung Disease

Tertiary	Atropine sulfate
	Atropine phosphate
Quaternary	Atropine methonitrate
	Flutropium bromide
	Glycopyrrolate
	Ipratropium bromide
	Oxytropium bromide

Table 2. Muscarinic Receptors in the Lung*

Receptor	Site	Action
M1	Parasympathetic ganglia	Facilitates synaptic transmission
	Mucous glands	Increases fluid
	Alveolar region	?
M2	Bronchial smooth muscle	Inhibits acetylcholine release
	Peripheral lung	?
M3	Bronchial smooth muscle	Constricts
	Mucous glands	Increases fluid

*There is conflicting evidence in the literature in animal and human studies concerning other sites and the action of the receptors within the lung. This table represents information from several sources.[1-4]

receptor is found in abundance in large airway smooth muscle and in mucous glands.[2] It is also found in smaller airways and throughout the lungs in small quantities. M3 receptors are also found in cells that play a role in inflammation. Blocking M3 activity promotes airway dilation. Activation of the M3 receptor by acetylcholine causes bronchoconstriction and increased mucus. Vagal (parasympathetic) nerve stimulation also causes activation of these M3 receptors. This is associated with an increase in mucus and a change in respiratory tract fluid to a thinner consistency. Vagal nerve excitation of bronchial smooth muscle normally occurs during expiration. This causes airway tone to increase through activation of the M3 receptor. This airway tone helps prevent collapse of airways that are not supported by cartilage, and improves the tone of cartilaginous airways. Although bronchial constriction can cause airway obstruction, a small amount of tone of the muscle in the airways helps maintain patent airways. This is considered to be the purpose of vagal (muscarinic) innervation of the airway muscles. Vagal muscarinic activity helps produce muscle tone so that the airways do not collapse during expiration. Excessive vagal parasympathetic tone may cause at least part of the airway obstruction seen in disease. An M2 receptor is also found at the terminal part of the nerve. Activation of the M2 receptor decreases the release of acetylcholine from the nerve; it is the feedback inhibitor of the transmission of the acetylcholine from the nerve to the mucous gland or muscle M3 receptors.

Antimuscarinic Drug Effects in the Lung

The ideal antimuscarinic drug to treat airways disease would block the M1 and airway smooth muscle M3 receptor but would not block the M2 receptor. Selective blockade of the M2 receptor would lead to airway obstruction by unregulated stimulation of the M3 receptors. However, the currently available drugs are not selective. They block the M3 receptor, resulting in bronchodilation, but also causing drying of the mucus. They also block the feedback inhibitor M2 receptor. There is no evidence that blocking the M2 receptor with current drugs causes any harm, because they also block the M1 and M3 receptor. The site of the bronchodilation is also an issue. The bulk of the M3 smooth muscle receptors are in the tracheal and large airway smooth muscle where vagal cholinergic innervation occurs.[2] Most of the bronchodilation associated with muscarinic antagonist therapy is in the larger airways.[3] However, relaxation of more peripheral airways also occurs, but not to the extent seen with β agonist therapy.[5] Also, there are larger numbers of muscarinic receptors in peripheral lung tissue.[4] The role of these receptors is not known, especially since there is no parasympathetic innervation to these areas.

The mechanism by which antimuscarinic therapy helps relieve dyspnea in people with lung disease is not completely understood. As noted above, these drugs dilate the larger airways and to a smaller extent relax the more distal airway smooth muscle. One of the more interesting phenomena seen with muscarinic antagonist therapy is the occasional person who has a remarkable increase in vital capacity. One explanation for this would be a substantial bronchodilation of the peripheral airways, but information to prove this is not available in the literature. There may be an unexplained mechanism by which these drugs relieve dyspnea, perhaps by blockade of muscarinic receptors at other sites within the lung.

Long-term use of inhaled antimuscarinic drugs is well tolerated.[6] Inhaled β agonist therapy is also well tolerated, but is associated with decreased efficacy with long-term use. This development of tolerance (often referred to as tachyphylaxis) is not seen with muscarinic antagonists.[6] The antimuscarinic drugs maintain their efficacy over the long term.

Use of Antimuscarinic Therapy in Obstructive Airway Disease

Antimuscarinic therapy with ipratropium has become first line therapy to treat chronic obstructive pulmonary

disease (COPD).[7] For the patient with mild symptomatic or moderate disease, inhaled antimuscarinic therapy may be all that is required. Muscarinic antagonists are not as effective as β agonists for the treatment of asthma. When added to maximal doses of β agonists, ipratropium may not cause further bronchodilation in these persons.[8] However, in some individuals, the addition of ipratropium to smaller doses of β agonists can provide bronchodilation without substantial adverse effects. The National Asthma Education and Prevention Program Guidelines[9] list ipratropium as an alternative for patients who are intolerant of β agonists or who need additional bronchodilation. Few studies have been done in asthmatic patients, but some published reports show that large doses of inhaled atropine or ipratropium can improve patients with severe exacerbations.[10] Inhaled β agonists are thought to be better tolerated and more standard drug therapy for these individuals. Antimuscarinic therapy has also been reported to help cystic fibrosis patients.[11]

Current Antimuscarinic Therapy

Ipratropium bromide is used throughout the world to treat patients with airways obstruction. In laboratory studies, ipratropium causes less salivary drying than other quaternary drugs, so it is the drug most used as an inhaled bronchodilator. It has a fast onset of action, but it doesn't peak as quickly as most β agonists. Its peak effect is at 1–2 hours in most individuals. It is effective in COPD patients.[6] A usual dosing interval for ipratropium is 6 hours. Some individuals have a better improvement in vital capacity than in forced expiratory volume in the first second. The usual recommended dose is 40–80 μg (2–4 puffs) from a metered-dose inhaler (MDI). Certain patients may require up to 8 puffs per treatment. Ipratropium is also available as a solution for small-volume nebulizer therapy. The dose given by this method is 500 μg. One interesting study on this product compared the efficacy of two nebulizers in administering the medication.[12] The authors found that an inefficient nebulizer was just as effective as a nebulizer that produced uniformly smaller aerosol particles. Since the drug works mainly on the larger airways, it is postulated that the characteristics of the aerosol were not as important as with a β agonist aerosol, for which the more efficient nebulizer was shown to produce better bronchodilation. Glycopyrrolate solution is also used for nebulizer therapy, although this is not an approved use.[13] The dose is the same as for ipratropium aerosol. Similarly, atropine sulfate has also been used, but the dose is twice that of ipratropium.[14] The safety of atropine and glycopyrrolate is not proven for long-term therapy, although there are published reports on their use.[13,14]

Combination Therapy

The routine combination therapy of ipratropium and albuterol is occasionally given to patients with moderate to severe COPD.[15] This combination therapy works better than either drug given alone, without the additional adverse effects that might be seen with maximal doses of either drug. Another advantage of combination therapy is that it simplifies therapy for persons who take multiple inhalers. Combination therapy is not commercially available as an aerosol solution, but the two medications can be premixed for patient convenience. An interesting result of the studies on combination therapy is that tolerance to the β agonist drug does not seem to develop in COPD patients, and the clinical efficacy appears to be better than if patients use separate MDIs.[15] The combination MDI can also be used as rescue therapy for dyspnea occurring at times between the regularly scheduled doses.[16]

New Antimuscarinic Drugs

There are newly synthesized antimuscarinic drugs that are more selective for the M3 and M1 sites, or have a rapid dissociation from the M2 site. These drugs would selectively cause bronchodilation, but might also cause more mucosal drying. In addition, the newer agents have a longer action, up to several days. Most of these drugs are being developed either as inhaled or oral therapy, depending on the drug's chemical properties. One new drug that is close to submission for approval is tiotropium, which is in the form of an inhaled powder.[17] It is taken once a day and has its peak effect after 3–6 days of therapy. Tiotropium has such a long half-time elimination that drug effect is present 24 hours after a dose. If the patient takes another dose at that time, there is an additional, but smaller, bronchodilator effect. Pulmonary function improvement peaks at 2–3 hours after a dose of tiotropium. Its bronchodilator effect wanes more slowly than ipratropium. At 24 hours following a dose of medication, forced expiratory volume in the first second values are on average about 10% above baseline values. After 4–5 days of therapy, the patient reaches a plateau of bronchodilation that is maintained by the daily inhalations.

Summary

Anticholinergic therapy is directed toward muscarinic receptors within the lung. Inhaled quaternary muscarinic antagonists are used because they cause less systemic adverse effects than other types of antimuscarinic drugs. Of the 5 possible muscarinic receptors, the lung contains three: M1, M2, and M3. Antagonism of the M1 and M3 receptors results in bronchodilation, primarily in the larger airways. The efficacy of the antimuscarinic bronchodilators cannot

be entirely explained by this mechanism, and there is probably peripheral activity as well. The use of inhaled antimuscarinic drugs is well tolerated, and the efficacy is maintained with chronic use. Although ipratropium is the first-line therapy for symptomatic COPD, it and other similar drugs can also be used to treat other obstructive diseases. Ipratropium is available in an MDI, in solution for small-volume nebulizer, and in combination with albuterol in an MDI. Newer antimuscarinic agents are being developed that are more selective for the M1 and M3 sites and last longer. Research is continuing to better understand the sites of action of these agents as well as to develop even more effective drugs.

REFERENCES

1. White MV. Muscarinic receptors in human airways (review). J Allergy Clin Immunol 1995;95(5 Pt 2):1065–1068.
2. Emala CW, Aryana A, Levine MA, Yasuda RP, Satkus SA, Wolfe BB, Hirshman CA. Expression of muscarinic receptor subtypes and M2-muscarinic inhibition of adenylyl cyclase in the lung. Am J Physiol 1995;268(1 Pt 1):L101–L107.
3. Douglas NJ, Sudlow MF, Flenley DC. Effect of an inhaled atropinelike agent on normal airway function. J Appl Physiol 1979;46(2):256–262.
4. Pistelli R, Patalano F, Liberatore SM, Incalzi RA, Ciappi G. Selectivity of anticholinergic drugs on central and peripheral airways in normal subjects. Eur J Respir Dis Suppl 1983;128(Pt 2):499–502.
5. Haddad EB, Mak JC, Belvisi MG, Nishikawa M, Rousell J, Barnes PJ. Muscarinic and β-adrenergic receptor expression in peripheral lung from normal and asthmatic patients. Am J Physiol 1996;270(6 Pt 1):L947–L953.
6. Tashkin DP, Ashutosh K, Bleecker ER, Britt EJ, Cugell DW, Cummiskey JM, et al. Comparison of the anticholinergic bronchodilator ipratropium bromide with metaproterenol in chronic obstructive pulmonary disease: a 90-day multi-center study. Am J Med 1986;81(5A):81–90.
7. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease (review). Am J Respir Crit Care Med 1995;152(5 Pt 2):S77–S121.
8. Chaieb J, Belcher N, Rees PJ. Maximum achievable bronchodilatation in asthma. Respir Med 1989;83(6):497–502.
9. National Asthma Education and Prevention Program. Expert Panel Report 2: Guidelines for the diagnosis and management of asthma. Bethesda, 1997; National Institutes of Health, NHLBI, NIH Publication No. 97–4051. Available at: www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm Accessed June 6, 2000.
10. Lanes SF, Garrett JE, Wentworth CE 3rd, Fitzgerald JM, Karpel JP. The effect of adding ipratropium bromide to salbutamol in the treatment of acute asthma: a pooled analysis of three trials. Chest 1998; 114(2):365–372.
11. Sanchez I, De Koster J, Holbrow J, Chernick V. The effect of high doses of inhaled salbutamol and ipratropium bromide in patients with stable cystic fibrosis. Chest 1993;104(3):842–846.
12. Johnson MA, Newman SP, Bloom R, Talaee N, Clarke SW. Delivery of albuterol and ipratropium bromide from two nebulizer systems in chronic stable asthma: efficacy and pulmonary deposition. Chest 1989;96(1):6–10.
13. Tzelepis G, Komanapolli S, Tyler D, Vega D, Fulambarker A. Comparison of nebulized glycopyrrolate and metaproterenol in chronic obstructive pulmonary disease. Eur Respir J 1996;9(1):100–103.
14. Marini JJ, Lakshminarayan S, Kradjan W. Atropine and terbutaline aerosols in chronic bronchitis: efficacy and sites of action. Chest 1981;80(3):285–291.
15. COMBIVENT Inhalation Aerosol Study Group. In chronic obstructive pulmonary disease, a combination of ipratropium and albuterol is more effective than either agent alone: an 85-day multicenter trial. Chest 1994;105(5):1411–1419.
16. Campbell S. For COPD a combination of ipratropium bromide and albuterol sulfate is more effective than albuterol base. Arch Intern Med 1999;159(2):156–160.
17. Littner M, Auerbach D, Campbell S, et al. The bronchodilator effects of tiotropium in stable COPD (abstract). Am J Respir Crit Care Med 1997;155:A282.

Evaluating the Efficacy of Mucoactive Aerosol Therapy

Mamta Fuloria MD and Bruce K Rubin MD

Introduction
Medications for Clearing Secretions
Mucolysis
Classic Mucolytic Agents
Peptide Mucolytics
Nondestructive Mucolysis
Mucokinesis
Mucoregulatory Agents
Aerosol Delivery of Mucoactive Agents
N-acetyl L-cysteine
Dornase Alfa
Osmolar Agents
Surfactant
Anti-inflammatory Agents
Combination Therapy
Clinical Use of Aerosol Mucoactive Agents
Future Development
Summary [Respir Care 2000;45(7):868–873] *Key words: mucus, mucociliary clearance, cough, asthma, cystic fibrosis, bronchitis, mucolytics, mucokinetics, mucoactive, aerosol.*

Introduction

Respiratory tract secretions consist of mucus, surfactant, and periciliary fluid. The airway surface fluid is present as a bilayer with a superficial gel or mucus layer and a layer of periciliary fluid interposed between the mucus layer and the epithelium. A thin layer of surfactant separates the mucus and periciliary fluid layers.[1] The mucus layer extends from the intermediate to the upper airway and is approximately 2–10 μm thick in the trachea. Airway mucus is the secretory product of the goblet cells (mucous cells of the pseudostratified columnar epithelium) and the submucosal glands. It is a nonhomogeneous, adhesive, viscoelastic gel composed of water, carbohydrates, proteins, and lipids. In health, the mucus gel is primarily composed of a 3-dimensional tangled polymer network of mucous glycoproteins or mucin. Mucin macromolecules are 70–80% carbohydrate, 20% protein, and 1–2% sulfate bound to oligosaccharide side chains. The protein backbones of mucins are encoded by MUC genes, at least 5 of which are expressed in the respiratory tract, although MUC5ac and MUC5b appear to be the predominant mucins in the lower respiratory tract.[2]

The depth and composition of the airway surface fluid depend on secretion from the mucous cells and submucous glands and active ion transport across the surface epithelium as a mechanism for altering the hydration of secretions. The composition and physical characteristics of airway surface fluid allow for normal ciliary function and airway hygiene,[3] and protect the airway from drying. Lysozyme, immunoglobulins, and antibacterial peptides in airway surface fluid provide a defense mechanism for the airways.

Mucus is transported from the lower respiratory tract into the pharynx by air flow and mucociliary clearance. Expec-

Mamta Fuloria MD and Bruce K Rubin MD are affiliated with the Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem, North Carolina.

A version of this paper was presented by Dr Rubin during the New Horizons Symposium, "Clinical Pharmacology of Inhaled Agents for the Respiratory Care Clinician," at the American Association for Respiratory Care's 45th International Respiratory Congress, December 14, 1999, in Las Vegas, Nevada.

Correspondence: Bruce K Rubin MD, Department of Pediatrics, Wake Forest University School of Medicine, Winston-Salem NC 27157-9229. E-mail: brubin@wfubmc.edu.

torated sputum is composed of lower respiratory tract secretions along with nasopharyngeal and oropharyngeal secretions, cellular debris, and microorganisms. Disruption of normal secretion or mucociliary clearance results in impaired pulmonary function and lung defense, and increased risk of infection.[4] Abnormal respiratory secretions can cause mucus inspissation, postobstructive atelectasis, and airway and parenchymal lung injury with bronchiectasis and pulmonary fibrosis, leading to severe pulmonary dysfunction.

Medications for Clearing Secretions

Medications that enhance the clearance of secretions from the respiratory tract or decrease the volume of respiratory secretions are collectively called mucoactive agents (Table 1).

Table 1. Mucoactive Agents

Mucoactive Agent	Potential Mechanisms of Action
Classical mucolytics	
N-acetylcysteine	Alters the chemical structure of disulfide containing proteins and peptides
Nacystelyn	Increases mucus chloride content (improved hydration of secretions) and severs disulfide bonds
Peptide mucolytics	
Dornase alfa	Hydrolyzes DNA molecules with reduction in DNA length
Gelsolin	Depolymerizes F-actin
Thymosin β4	Depolymerizes F-actin
Nondestructive mucolytics	
Hypertonic saline	Reduces ionic bonds and increases secretion hydration
Dextran	Breaks hydrogen bonds and increases secretion hydration
Low molecular weight heparin	May break both hydrogen and ionic bonds
Mucoregulatory agents	
Anticholinergic agents	Decreases volume of stimulated secretions
Glucocorticoids	Decreases airway inflammation and mucin secretion
Indomethacin	Decreases airway inflammation
Macrolide antibiotics	Decreases airway inflammation and mucin secretion
Mucokinetic agents	
Bronchodilators	Can improve cough clearance by increasing expiratory flow
Surfactants	Decreases sputum adhesiveness

Mucolysis

Mucociliary clearance is in part dependent on the viscoelasticity of the secretions. Mucolysis involves disruption of the cross-linking or tangled interaction between the macromolecules that form the gel. Normally, reduction in cross-linking and viscoelasticity of the mucus gel improve mucociliary clearance. However, occasionally, the mucus may be too thin for effective clearance.[5] In such an instance, increasing the cross-linking with a mucospissic agent may improve clearance. These agents collectively are called mucotropic agents.

Classic Mucolytic Agents

Classic mucolytic agents work by severing disulfide bonds, calcium binding, depolymerizing mucopolysaccharides, and liquefying proteins. Agents containing free sulfhydryl (thiol) groups reduce the disulfide bridges interconnecting cysteine residues on adjacent mucin proteins. These include N-acetyl L-cysteine (NAC). NAC reduces the disulfide bond, thus reducing the elasticity and viscosity of the mucus gel.[6,7] In vitro studies have demonstrated a dose-dependent effect of NAC on the viscoelastic properties of secretions.[8] In vivo, it is ineffective when given orally.[9]

Peptide Mucolytics

Sputum contains products of inflammation, including cellular debris and neutrophil-derived DNA and filamentous actin (F-actin). DNA and F-actin copolymerize to form a rigid polymer network entangled with the mucin gel.[10] Peptide mucolytics degrade these abnormal filaments and leave the glycoprotein network relatively intact. Dornase alfa has been approved for the treatment of cystic fibrosis. It cleaves DNA polymers, reducing both sputum viscosity and adhesivity.[11] Other peptide mucolytics under investigation include the F-actin depolymerizing agents gelsolin and thymosin β4. In vitro studies have demonstrated that F-actin depolymerizing agents in conjunction with dornase alfa result in a greater reduction in sputum viscoelasticity and cohesivity.[12,13] The F-actin depolymerizing agents both destabilize the actin-DNA filament network and increase the depolymerizing activity of dornase alfa on the DNA filaments.

Nondestructive Mucolysis

Although agents that affect ionic charge interactions and hydrogen bonds are not true mucolytic agents, they can alter polymer interactions, reducing both viscosity and elasticity without reducing the polymer chain length. These agents include both ionic agents such as sodium chloride and nonionic agents such as dextran.

Ionic agents are thought to shield the fixed charges along the macromolecular core of the mucin polymer, making it less stiff and less extended, thus reducing the entanglements with neighboring macromolecules. Hyperosmolar saline breaks ionic bonds within the mucus gel, reducing the degree of cross-linking and the viscoelasticity of sputum.[14,15] It may also tonically increase the water content of mucus.[16] In the presence of infected mucus, hypertonic saline can separate the DNA molecules from the mucoprotein component of the mucus, making the mucoprotein susceptible to proteolytic enzyme digestion.

Agents that alter hydrogen bonding within mucus may improve mucus clearance.[17,18] Although each individual hydrogen bond is weak, the total potential of these bonds is substantial, since the oligosaccharide side chains make up about 80% of the mucin structure. The lower-molecular-weight fractions are primarily responsible for the mucoactive effects of dextran. In addition to the breakdown of hydrogen bonds, an osmotic effect with increased hydration of the mucus could also result in improved clearance of secretions.

Mucokinesis

For an effective cough, there must be adequate air flow to detach secretions from the epithelium and mobilize sputum so that it can be expectorated. Mucokinetic agents improve the cough clearance of secretions by increasing air flow or decreasing the interaction between secretions and epithelium.

Mucus adheres to the cilia and the epithelium. A layer of surfactant between the periciliary fluid and the mucus gel improves spreading of the mucus and promotes efficient energy transfer from the beating cilia to the mucus, thus preventing entanglement of cilia in mucus and promoting cough clearance of secretions. Phase 2 clinical trials using a surfactant aerosol demonstrated a significant increase in pulmonary function associated with improved in vitro mucus clearability in patients with cystic fibrosis and chronic bronchitis.[19]

Bronchodilators can be considered mucokinetic agents in those patients who demonstrate an improvement in air flow with bronchodilator therapy. By virtue of their ability to increase expiratory flow in intermediate and large airways, they can substantially improve cough clearance. Since β agonists are mucus secretagogues, it is important to demonstrate improvement in pulmonary function before these agents are prescribed. Although β agonists improve ciliary beat frequency, this does not appear to improve mucus clearance in patients with lung disease.

Mucoregulatory Agents

Agents that inhibit mucus production or secretion are called mucoregulatory agents. These include anticholinergic agents (decrease the volume of stimulated secretions without increasing viscosity), glucocorticosteroids, indomethacin, and some macrolide antibiotics. Reduction of mucin secretion by macrolide antibiotics (erythromycin and clarithromycin) is unrelated to their antibacterial activity but may be related, in part, to their anti-inflammatory properties.[20]

Aerosol Delivery of Mucoactive Agents

Most mucoactive agents have been developed as oral preparations. Oral medications are usually easy to administer and dosing is relatively precise, although absorption may be variable. Some medications, such as the macrolide antibiotics, appear to be effective only when given orally. Other drugs, such as guaifenesin, may best target effector cells if given orally. Ideally, oral mucoactive agents should be easily ingested and adequately absorbed from the gastrointestinal tract and should be effective in decreasing secretions or enhancing clearance. Often, systemically administered mucoactive agents may be only partially effective because of a poor therapeutic ratio. Therefore, in recent years, there has been an increasing trend toward targeting the airways directly by means of aerosol therapy. The potential advantages of inhaling mucoactive agents include localized action in the airways, more rapid onset of action, and decreased adverse effects. Peptide and protein compounds, which would otherwise be broken down in the stomach, can be administered via inhalation and often will retain activity.

Various mucoactive agents are being investigated for possible delivery via aerosol. These include NAC, dornase alfa, osmolar agents, surfactant, and anti-inflammatory agents. In patients with secretion retention, aerosolized drug delivery is affected by decreased drug transport across infected secretions, drug losses due to binding to glycoproteins, inactivation by various mucus components, and inefficient drug delivery to peripheral airways because of mucus plugging.

N-acetyl L-cysteine

In vitro studies have shown a dose-dependent effect of NAC on the viscoelasticity of sputum, such that the greater the concentration of NAC, the greater the reduction in secretion viscosity.[6,8] NAC also is an antioxidant by increasing glutathione. The use of NAC via aerosol is limited, since it can induce bronchospasm in some patients. It has an unpleasant taste and odor, making it unpopular with many patients. A systematic review of the use of nebulized NAC in patients with cystic fibrosis found only 3 randomized clinical trials, none of which showed a clinically relevant beneficial effect of therapy.[21,22] A lysine derivative of NAC, nacystelyn (NAL), can reduce mucus viscoelasticity in dogs[23] and in cystic fibrosis patients.[24] NAL im-

proves tracheal mucus velocity in anesthetized dogs, and this improvement is accompanied by an increase in mucus chloride content consistent with increased secretion hydration. NAL may be an attractive alternative to NAC, as it can be administered via pressurized metered dose inhaler and has a pseudoneutral pH, compared to that of nebulized NAC (pH 2.2). European clinical trials of aerosolized NAL are in progress.

Dornase Alfa

Recombinant human deoxyribonuclease I (rhDNase or dornase alfa) cleaves DNA molecules, resulting in decreased sputum viscosity and tenacity.[11] Administration of dornase alfa via aerosol to patients with stable cystic fibrosis lung disease has been shown to improve forced expiratory volume in the first second (FEV_1), reduce the frequency of pulmonary exacerbations, and improve the measured quality of life.[25] Ultrasonic devices denature peptides such as dornase alfa. Clearly, the choice of a nebulizer system for delivery of any drug depends on the physicochemical properties of the agent, dose of the drug, and patient compliance issues.

Osmolar Agents

Isotonic saline aerosol has been shown to induce expectoration (sputum induction) even in healthy subjects. Significant improvement in FEV_1 has been demonstrated after the use of hypertonic saline aerosol therapy by cystic fibrosis patients.[26] The response to hypertonic saline inhalation is dose-dependent, with better results seen with more concentrated saline solutions.[27] Patients with hyperreactive airways may have bronchospasm following administration of hypertonic saline. Hypernatremia can result following administration of hypertonic saline in patients with renal insufficiency.

Secretion clearance can be stimulated by monosaccharides or disaccharides such as mannitol and lactose. A dry powder of mannitol has been used as an osmotic stimulus to increase mucociliary clearance in healthy subjects and in patients with asthma and bronchiectasis.[17] Mannitol inhalation increases mucociliary clearance, and the response is comparable to that obtained by inhalation of hypertonic saline. The increase in secretion clearance was not related to induced cough. Dextran administration via aerosol has also been shown to increase tracheal mucus velocity in dogs.[28]

Low-molecular-weight heparin, a charged oligosaccharide, may have greater mucolytic and mucokinetic properties than dextran. It may disrupt hydrogen bonds similar to low-molecular-weight dextran, and improve ionic interactions like hypertonic saline. Aerosolized low-molecular-weight heparin also shows promise in the treatment of asthma, presumably by interfering with antigen-receptor binding.[29]

Surfactant

Pulmonary surfactants help maintain bronchiolar and alveolar stability, particularly at low lung volumes. In the airway, surfactant can provide lubrication, increase cilia beat frequency, and improve interaction between cilia and secretions, resulting in improved cough and mucociliary clearance. Airway surfactant facilitates the formation of an interfacial bilayer that helps transfer kinetic energy between the cilia and the mucus layer.

Direct tracheal instillation of surfactant is impractical for most patients with reduced mucociliary clearance. This mode of surfactant delivery is also expensive and inefficient because of nonuniform distribution of surfactant, necessitating administration of large volumes of the drug. An appealing alternative is administration of surfactant via aerosol. Whereas surfactant instillation did not improve severe ventilation-perfusion mismatch in an isolated lung model of acute lung injury, nebulized surfactant markedly reversed it.[30] Surfactant aerosol therapy has also been shown to improve both in vitro mucociliary clearability of sputum and pulmonary function in patients with chronic bronchitis or cystic fibrosis.[19]

Meconium aspiration syndrome is a disease characterized by mechanical obstruction of the airways, inflammation and chemical pneumonitis, and inactivation of surfactant function, and this can lead to pulmonary hypertension.[31] These infants are often treated with surfactant therapy. Those infants not sick enough to require intubation but requiring supplemental oxygen may benefit from inhaled surfactant therapy. Surfactant inhalation appears to be a promising new approach for providing surfactant therapy.

Anti-inflammatory Agents

Anti-inflammatory agents reduce airway mucosal inflammation, and may decrease secretion production and retention. In inflammatory airway disease, epithelial cell desquamation results in increased secretions. The increase in proteases, DNA, and F-actin increase mucus viscosity and decrease mucociliary clearance. Although low-dose oral corticosteroids improve the clinical course of selected cystic fibrosis patients,[32] clinical trials of inhaled corticosteroids have shown conflicting results. Another anti-inflammatory agent, indomethacin, administered via nebulizer, effectively reduced mucus hypersecretion in diffuse panbronchiolitis patients.[33] Airway targeted antioxidant and antiprotease therapies, if effective, could decrease airway secretion volume and purulence.

Combination Therapy

Combination therapy may consist of different medications aerosolized together or in tandem. The most commonly used combination therapy in cystic fibrosis patients is the combination of antibiotics and bronchodilators. Another possible combination is NAL with dornase alfa:[34] combination therapy at half the concentration of each drug significantly decreased in vitro cystic fibrosis sputum cohesivity, indicating an additive effect of the two drugs. Similar effects were observed when dornase alfa was used in conjunction with either hypertonic saline[14] or gelsolin.[12,13] The use of combination therapy may decrease the number of doses of medications taken through the day, with possible improvement in patient compliance. The clinical efficacy of combination therapy needs to be further evaluated in clinical trials. Where feasible, therapeutic agents to be delivered via inhalation should be formulated for delivery from a pressurized metered-dose inhaler or a dry powder inhaler, since these are more patient-friendly, easier to use, and usually more cost effective.

Clinical Use of Aerosol Mucoactive Agents

The principal indication for the use of mucoactive agents is to reduce airway obstruction by abnormal secretions. Decreasing the volume of airway secretions can reduce gas trapping and improve the performance of the muscles of respiration. The use of mucoactive therapy to decrease secretion volume or to increase mucus clearance should be considered only after initiation of therapy directed at decreasing infection and inflammation and after minimizing exposure to irritants, including tobacco smoke.

Patients most likely to benefit from mucoactive therapy usually have preserved air flow and a history of increased airway secretions. In general, with an FEV_1 of $< 25\%$ of predicted, it becomes difficult to expectorate secretions. When air flow is severely compromised, mucolytic agents could theoretically reduce sputum clearance because of retrograde flow. During episodes of acute mucus retention (eg, acute bronchitis or acute exacerbation of cystic fibrosis), mucoactive agents may be less likely to be effective. The decreased responsiveness of patients to mucoactive therapy may be related to reduced air flow with infection and muscular weakness that can further compromise air flow-dependent clearance. Patients who are unable to protect their airways may be unable to handle increased airway secretions.

The effectiveness of mucoactive therapy can be difficult to assess. When there is an improvement in symptoms and air flow or reduced gas trapping, the benefit of therapy is clear. However, changes in FEV_1 poorly reflect clinical improvement with mucoactive agents. Expectorated sputum volume is not a good measure of the effectiveness of mucoactive therapy. This is partly related to the limitations in accurately measuring the volume of expectorated sputum because of patient reluctance or inability to expectorate, swallowing of secretions, and salivary contamination. Sputum volume also varies from day to day, and at different times of the day. Finally, increased sputum could reflect either increased clearance or increased production of secretions.

The scientific evaluation of secretion properties and the clinical response to therapy will facilitate the development of effective mucoactive therapy and help us to better determine which patients are most likely to benefit from specific therapies.

Future Development

With improved understanding of the role of mucoactive agents in various inflammatory conditions, it will be possible to develop more effective therapies. Because of targeted action in the airways with the possibility of fewer adverse effects, there is increasing interest in delivering therapies at the site of disease in the airways. Improvements in aerosol delivery systems will result in improved aerosol efficiency. Appropriate drug formulations need to be developed that can be easily dispersed using our current delivery systems and systems that will soon be available. Another treatment modality of the future is likely to be gene transfection to treat diseases such as cystic fibrosis. Both cystic fibrosis gene cDNA liposomes[35] and modified adenoviral vectors[36] have been evaluated in patients with cystic fibrosis.

Summary

The aerosol route is attractive for the delivery of mucoactive medications. Mucoactive medications include mucolytics, which depolymerize polymers of mucin (classic mucolytics) or DNA/actin (peptide mucolytics), mucokinetic agents, which increase cough clearance, mucoregulatory medications, which decrease abnormal mucus secretion, and expectorants and ion channel modifiers.

Despite the widespread use of these medications, there are few well conducted studies and thus few data clearly supporting (or failing to support) their use. This will change as our understanding of mucociliary physiology and pharmacology increases and as well designed and well powered clinical trials are conducted with appropriate outcome measurements.

Effective mucoactive therapy should make a profound impact on the care of patients with chronic bronchitis, asthma, cystic fibrosis, and inflammatory airways disease, and will be essential for the effective delivery of gene therapy vectors and bioactive peptides to the airway epithelium.

REFERENCES

1. Morgenroth K, Bolz J. Morphological features of the interaction between mucus and surfactant on the bronchial mucosa. Respiration 1985;47(3):225–231.
2. Gendler SJ, Spicer AP. Epithelial mucin genes (review). Annu Rev Physiol 1995;57:607–634.
3. King M, Rubin BK. Rheology of airway mucus: relationship with clearance function. In: Takashima T, Shimura S, editors. Airway secretion: physiological bases for the control of mucus hypersecretion. New York: Marcel Dekker; 1994: 283–314.
4. Wanner A, Salathé M, O'Riordan TG. Mucociliary clearance in the airways (review). Am J Respir Crit Care Med 1996;154(6 Pt 1): 1868–1902.
5. Rubin BK, MacLeod PM, Sturgess J, King M. Recurrent respiratory infections in a child with fucosidosis: is the mucus too thin for effective transport? Pediatr Pulmonol 1991;10(4):304–309.
6. Sheffner AL. The reduction in vitro in viscosity of mucoprotein solutions by a new mucolytic agent, N-acetylcysteine. Ann NY Acad Sci 1963;106:298–310.
7. Davis SS, Scobie S, Inglis A. The effect of sulphydryl compounds and cross linking agents on the viscous and visoelastic properties of mucus. Biorheology 1975;12(3–4):225–232.
8. Lieberman J. Measurement of sputum viscosity in a cone-plate viscometer. II. An evaluation of mucolytic agents in vitro. Am Rev Respir Dis 1968;97(4):662–672.
9. Clarkson L, Okamoto K, Azizi F, Kim JS, Ward A, Wu Q, Rubin BK. N-acetylcysteine (NAC) therapy has no effect on pulmonary function, quality of life or the biophysical properties of sputum from patients with stable chronic bronchitis (abstract). Am J Respir Crit Care Med 1999;159:A815.
10. Tomkiewicz RP, Kishioka C, Freeman J, Rubin BK. DNA and actin filament ultrastructure in cystic fibrosis sputum. In: Baum G, editor. Cilia, mucus and mucociliary interactions. New York: Marcel Dekker; 1998: 333–341.
11. Shak S, Capon DJ, Hellmiss R, Marsters SA, Baker CL. Recombinant human DNase I reduces the viscosity of cystic fibrosis sputum. Proc Natl Acad Sci USA 1990;87(23):9188–9192.
12. Vasconcellos CA, Allen PG, Wohl ME, Drazen JM, Janmey PA, Stossel TP. Reduction in viscosity of cystic fibrosis sputum in vitro by gelsolin. Science 1994;263(5149):969–971.
13. Dasgupta B, Tomkiewicz RP, De Sanctis GT, Boyd WA, King M. Rheological properties in cystic fibrosis airway secretions with combined rhDNase and gelsolin treatment. In: Singh M, Savena VP, editors. Advances in physiological fluid dynamics. New Delhi: Narosa; 1996: 74–78.
14. King M, Dasgupta B, Tomkiewicz RP, Brown NE. Rheology of cystic fibrosis sputum after in vitro treatment with hypertonic saline alone and in combination with recombinant human deoxyribonuclease I. Am J Respir Crit Care Med 1997;156(1):173–177.
15. Wills PJ, Hall RL, Chan W, Cole PJ. Sodium chloride increases the ciliary transportability of cystic fibrosis and bronchiectasis sputum on the mucus-depleted bovine trachea. J Clin Invest 1997;99(1):9–13.
16. Winters SL, Yeates DB. Role of hydration, sodium, and chloride in regulation of canine mucociliary transport system. J Appl Physiol 1997;83(4):1360–1369.
17. Daviskas E, Anderson SD, Brannan JD, Chan HK, Eberl S, Bautovich G. Inhalation of dry-powder mannitol increases mucociliary clearance. Eur Respir J 1997;10(11):2449–2454.
18. Shibuya Y, Wills PJ, Kitamura S, Cole PJ. The effects of lactose on mucociliary transportability and rheology of cystic fibrosis and bronchiectasis sputum. Eur Respir J 1997;10:321s.
19. Anzueto A, Jubran A, Ohar JA, Piquette CA, Rennard SI, Colice G, et al. Effects of aerosolized surfactant in patients with stable chronic bronchitis: a prospective randomized controlled trial. JAMA 1997; 278(17):1426–1431.
20. Tamaoki J, Takeyama K, Yamawaki I, Kondo M, Konno K. Lipopolysaccharide-induced goblet cell hypersecretion in the guinea pig trachea: inhibition by macrolides. Am J Physiol 1997;272(1 Pt 1): L15–L19.
21. Howatt WF, DeMuth GR. A double-blind study of the use of acetylcysteine in patients with cystic fibrosis. Univ Mich Med Cent J 1966;32(2):82–85.
22. Teclin JS, Holsclaw DS Jr. Bronchial drainage with aerosol medications in cystic fibrosis. Phys Ther 1976;56(9):999–1003.
23. Tomkiewicz RP, App EM, De Sanctis GT, Coffiner M, Maes P, Rubin BK, King M. A comparison of a new mucolytic N-acetylcysteine L-lysinate with N-acetylcysteine: airway epithelial function and mucus changes in dog. Pulm Pharmacol 1995;8(6):259–265.
24. App EM, Baran D, Dab I, Mafroot A, Coffiner M, Maes P, et al. Efficacy, safety and tolerability of chronic inhalation therapy with Nacystelyn R vs. placebo in cystic fibrosis patients (abstract). Am J Respir Crit Care Med 1997;155(4 Pt 2):A199.
25. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in cystic fibrosis. The Pulmozyme Study Group. N Engl J Med 1994;331(10):637–648.
26. Eng PA, Morton J, Douglass JA, Riedler J, Wilson J, Robertson CF. Short-term efficacy of ultrasonically nebulized hypertonic saline in cystic fibrosis. Pediatr Pulmonol 1996;21(2):77–83.
27. Robinson M, Hemming AL, Regins JA, Wong AG, Bailey DL, Bautovitch GJ, et al. Effect of increasing doses of hypertonic saline on mucociliary clearance in patients with cystic fibrosis. Thorax 1997;52(10):900–903.
28. Feng W, Garrett H, Speert DP, King M. Improved clearability of cystic fibrosis sputum with dextran treatment in vitro. Am J Respir Crit Care Med 1998;157(3 Pt 1):710–714.
29. Ahmed T, Garrigo J, Danta I. Preventing bronchoconstriction in exercise-induced asthma with inhaled heparin. N Engl J Med 1993; 329(2):90–95.
30. Schermuly R, Schmehl T, Gunther A, Grimminger F, Seeger W, Walmrath D. Ultrasonic nebulization for efficient delivery of surfactant in a model of acute lung injury: impact on gas exchange. Am J Respir Crit Care Med 1997;156(2 Pt 1):445–453.
31. Fuloria M, Wiswell TE. Resuscitation of the meconium-stained infant and prevention of meconium aspiration syndrome (review). J Perinatol 1999;19(3):234–241.
32. Eigen H, Rosenstein BJ, FitzSimmons S, Schidlow DV. A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. Cystic Fibrosis Foundation Prednisone Trial Group. J Pediatr 1995;126(4):515–523.
33. Tamaoki J, Chiyotani A, Kobayashi K, Sakai N, Kanemura T, Takizawa T. Effect of indomethacin on bronchorrhea in patients with chronic bronchitis, diffuse panbronchiolitis, or bronchiectasis. Am Rev Respir Dis 1992;145(3):548–552.
34. Dasgupta B, King M. Reduction in viscoelasticity in cystic fibrosis sputum in vitro using combined treatment with nacystelyn and rhDNase. Pediatr Pulmonol 1996;22(3):161–166.
35. Schreier H, Gagne L, Conary JT, Laurian G. Simulated lung transfection by nebulization of liposome cDNA complexes using a cascade impactor seeded with 2-CFSMEO-cells. J Aerosol Med 1998;11(1):1–13.
36. Bellon G, Michel-Calemard L, Thouvenot D, Jagneaux V, Poitevin F, Malcus C, et al. Aerosol administration of a recombinant adenovirus expressing CFTR to cystic fibrosis patients: a phase I clinical trial. Hum Gene Ther 1997;8(1):15–25.

Aerosol Device Selection: Evidence to Practice

James B Fink MS RRT FAARC

Introduction
Aerosol Generators
  Nebulizers
  Breath-Enhanced Nebulizer
  Intermittent Nebulization
  Breath-Actuated Nebulizer
Hospital Versus Home Use
Special Medication Delivery Issues for Infants and Children
Large-Volume Nebulizers
Ultrasonic Nebulizers
Pressurized Metered-Dose Inhalers
  Technique
  Accessory Devices
  Flow-Triggered Pressurized Metered-Dose Inhaler
  Spacers and Valved Holding Chambers
  Care and Cleaning
Dry Powder Inhalers
  Inspiratory Flow
Device Selection and Compliance
Summary [Respir Care 2000;45(7):874–885] *Key words: aerosol, metered-dose inhaler, dry powder inhaler, nebulizer, breath-actuated, breath-enhanced, spacer, holding chamber.*

Introduction

Selection of an appropriate aerosol device influences the success of therapy. A variety of factors should be considered when selecting an aerosol device (Table 1). In addition, the drug formulation and the setting for the treatment influence aerosol device selection. The incorrect use of aerosol devices is a major factor in suboptimal therapy. Consequently, patient education is essential for effective administration of aerosolized drugs and adherence to the medication plan.

Aerosol Generators

The most common methods of generating therapeutic aerosols are jet pneumatic nebulizer, ultrasonic nebulizer (USN), pressurized metered-dose inhaler (pMDI), and dry powder inhaler (DPI). Device selection should be an active process predicated upon the available formulations of medication, patient needs, and capabilities of the available technology.

Drug formulations dictate, in part, which aerosol options are available for medication delivery. Most solutions can be nebulized if the medication is soluble (corticosteroids are a notable exception), but the physical characteristics of the solution (or suspension) can affect particle size and nebulizer output. Because of development costs,

James B Fink MS RRT FAARC is affiliated with the Division of Pulmonary and Critical Care Medicine, Loyola University of Chicago Stritch School of Medicine, and Hines Veterans Hospital, Hines, Illinois, where this paper was written. He is now also affiliated with AeroGen, Sunnyvale, California.

A version of this paper was presented by Mr Fink during the New Horizons Symposium, "Clinical Pharmacology of Inhaled Agents for the Respiratory Care Clinician," at the American Association for Respiratory Care's 45th International Respiratory Congress, December 14, 1999, in Las Vegas, Nevada.

Correspondence: James B Fink MS RRT FAARC, AeroGen, 1310 Orleans Drive, Sunnyvale CA 94089. E-mail: jfink@aerogen.com.

Table 1. Factors Influencing Efficacy

Properties of the device
Properties of the medication
Characteristics of the aerosol
Technique of use
Type and severity of disease
Response to treatment
Patient acceptance/preference

many aerosol medications are initially developed as nebulizer solutions and later reformulated for pMDI or DPI.

Theoretically, if a particle can be milled to a respirable size while retaining bioactivity, it can be delivered via pMDI or DPI. At present, DPI formulations are limited to a few preparations, but with more effective DPI devices being developed it is anticipated that a greater variety of DPI medications and devices will soon be commercially available. There are still a greater variety of available formulations for pMDIs than for DPIs or conventional nebulizer, with more being developed for the new hydrofluoroalkane-propelled pMDIs.

Nebulizers

An effective small-volume pneumatic nebulizer (SVN) should deliver $>$ 50% of its total dose as aerosol in the respirable range of 1–5 μm mass median aerodynamic diameter (MMAD) in $\leq$ 10 minutes of nebulization time. Nebulizer performance varies with diluent volume, operating flow, pressures, gas density, and nebulizer model. The amount of drug that is nebulized increases as the volume of diluent is increased. The residual volume of medicine that remains in commercial SVNs varies from 0.8 mL to 1.5 mL, depending on the specific device, so increasing the fill volume allows a greater proportion of the active medication to be nebulized.[1]

The higher the gas flow to the nebulizer, the smaller the particle size generated and the shorter the time required to nebulize the full dose.[2] Within the limits of the design of the nebulizer, the higher the gas pressure and/or flow to the nebulizer, the smaller the particle size generated.[3] Nebulizers that produce smaller particles by use of baffles, such as one way valves, may have a lower total drug output per minute than the same nebulizer without baffling, requiring more time to deliver a standard dose of medication.

Gas density affects both aerosol generation and delivery of aerosol to the lungs. This is most evident with low density helium-oxygen (heliox) mixtures. The lower the density of a carrier gas, the less turbulent the flow (ie, the lower the Reynolds number), and this theoretically decreases aerosol impaction.[4] However, when heliox is used to drive a jet nebulizer, aerosol output is much less than with air or oxygen, requiring a 2-fold increase in flow to produce a comparable output of respirable aerosol per minute. Thus, though helium increases the amount of aerosol getting into the lungs, it impairs the production of the aerosol suspension at the nebulizer.[5]

Humidity and temperature affect the particle size and the concentration of drug remaining in the nebulizer. Evaporation of water and adiabatic expansion of gas can reduce the temperature of the aerosol to as much as 5° C below ambient temperature. Aerosol particles entrained into a warm and fully saturated gas stream increase in size. These particles can also coalesce, further increasing the MMAD and, in the case of a DPI, this can severely compromise the output of respirable-size particles.

With the large volume of the nominal dose that is trapped in conventional nebulizers, it is important to determine when to end the nebulizer treatment. Malone et al found that albuterol delivery from the nebulizer ceased following the onset of inconsistent nebulization (sputtering).[6] Aerosol output declined by one-half within 20 seconds of the onset of sputtering. The concentration of albuterol in the nebulizer cup increased significantly once the aerosol output declined, and further weight loss in the nebulizer was primarily due to evaporation. Aerosolization past the point of initial jet nebulizer sputter is ineffective, and should be used as an indication to end the treatment (Table 2).

Nebulizer selection affects aerosol delivery. Only nebulizers that have been shown to work reliably under specific conditions, with specific medications, and with specific compressors should be used.[7] Nebulizers that produce aerosols with MMADs of 0.5–3.0 μm are more likely to achieve greater deposition in the lower respiratory tract, especially

Table 2. Optimal Technique for Use of Small-Volume Nebulizer

Assemble apparatus.
Mix medication per prescription and add to nebulizer.
Assure that fill volume is 4-6 mL.
If SVN is operated continuously, add 50 mL of tubing or other reservoir.
Attach gas source, providing adequate gas flow to operate within specifications of the nebulizer.
Position patient in an upright position, sitting, or reclining.
Through mouthpiece or mask, encourage patient to breathe through mouth.
Through artificial or bypassed upper airway, assure that nebulizer is positioned appropriately and not placing undue pressure on the airway.
Encourage patient to take normal, comfortable breaths, with occasional deep breaths and low inspiratory flow.
Periodically tap nebulizer to return impacted particles to the reservoir.
Assess patient for comfort, adverse effects, and response throughout treatment.
When nebulizer begins to sputter and stops nebulizing, remove from patient and either clean/disinfect, replace, or rinse with sterile water and air dry, properly storing between treatments.

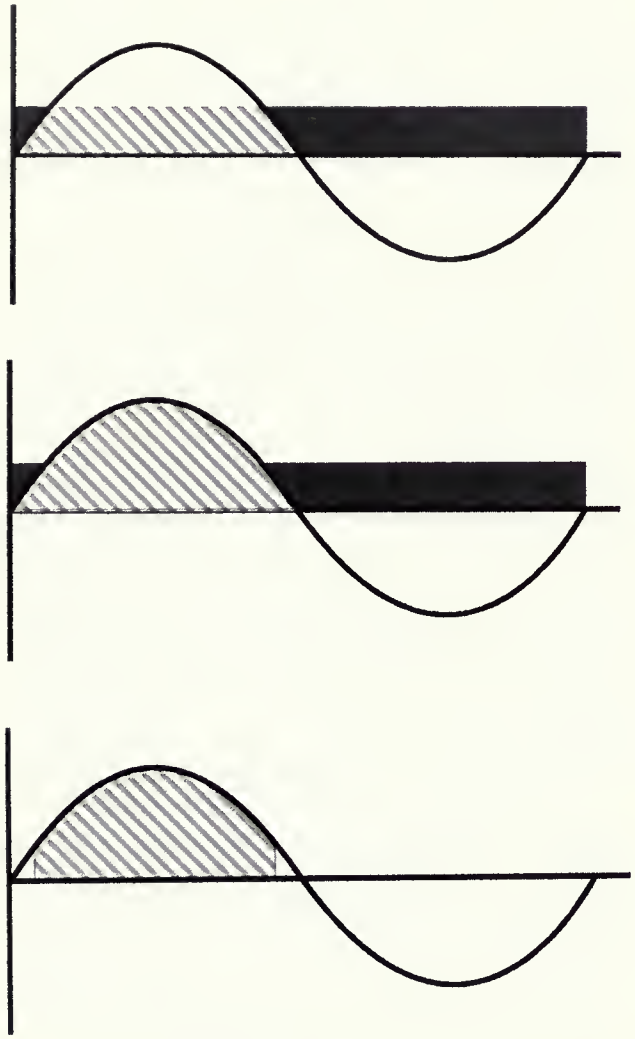


Fig. 1. Diagram of the aerosol emitted from a nebulizer in relation to inspiratory and expiratory cycles with (top) continuous, (middle) breath enhanced, and (bottom) breath-actuated nebulizers.

when used to treat small children or during mechanical ventilation.[8]

SVNs are commonly operated continuously. Continuous nebulization wastes medication because the aerosol produced between the end of an inspiration and the beginning of the next inspiration is largely lost to the atmosphere (Fig. 1). This is a major factor in the poor efficiency associated with pneumatic nebulizers. If only 50% of the nominal dose exits the nebulizer, with 60% of that as particles in the respirable size range, and only 25% of that is inhaled by the patient, then $\leq$ 10% of the nominal dose is inhaled by the patient (with 20% of that exhaled).

A reservoir on the expiratory limb of the nebulizer conserves drug aerosol by collecting some of the nebulizer output that would otherwise be wasted to the atmosphere.[9] Placing 6 inches of aerosol tubing on the expiratory side of the nebulizer T-tube may improve inhaled drug by > 20%.

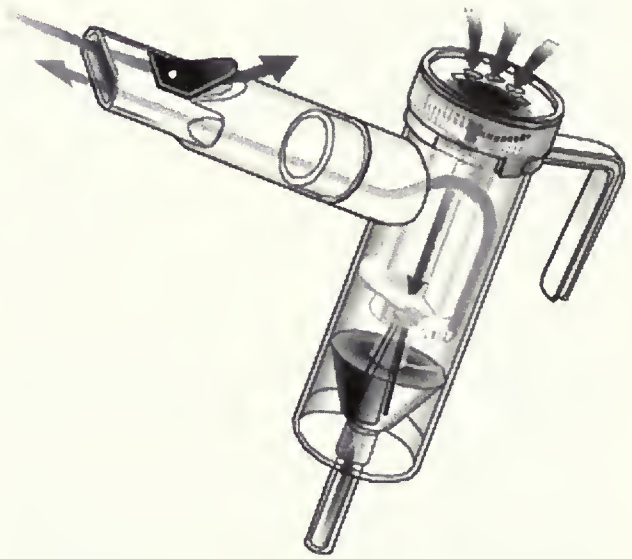


Fig. 2. An example of a breath-enhanced, vented nebulizer (PARI LC Plus). (Courtesy of PARI Respiratory Equipment Inc, Midlothian, Virginia.)

Alternatively, commercial devices with simple bag reservoirs allow a greater volume reservoir, in which the smaller aerosol particles remain in suspension for inhalation with the next breath, while larger particles rain out.

Breath-Enhanced Nebulizer

A vented nebulizer system can be used to reduce aerosol waste.[10] In this type of device (Fig. 2), an inspiratory vent allows the patient to inhale additional air with the aerosolized drug, increasing drug delivery on inspiration, whereas on exhalation, the inlet vent closes and aerosol exits via a one-way valve near the mouthpiece, reducing aerosol waste. This increases inhaled dose by as much as 20–50% without increasing the time required for the treatment.

Intermittent Nebulization

Intermittent nebulization, synchronizing aerosol generation with inspiration, greatly increases the amount of drug available for inspiration. Though the aerosol inhaled per breath during nebulization is similar, nebulization time increases by $\geq$ 4-fold, as does the total aerosol inhaled. Intermittent nebulization can be accomplished with a thumb control port that allows the patient to manually direct gas to the nebulizer only on inspiration. This improves efficiency of the nebulizer if the patient has good hand-breath coordination.

Breath-Actuated Nebulizer

Breath-actuated nebulization occurs when the aerosol is generated in coordination with inspiration. Nebulizing only

Fig. 3. Breath-actuated pneumatic nebulizers. Left: Halo*Lite* (Courtesy of Medic-Aid, West Sussex, United Kingdom.) Right: Aeroeclipse (Courtesy of Monaghan Medical, Syracuse, New York.)

during inspiration is more efficient than continuous or vented systems. Breath-actuated nebulizers deliver the same or greater dose in the same amount of time as the continuous nebulizer, though to nebulize the entire dose in the nebulizer, a breath-actuated system may take 3–4 times longer (delivering 3–4 times more drug) than a continuous nebulizer. The Halolite system uses a microprocessor and pressure sensor to nebulize during the first half of inspiration. This compressor-driven nebulizer (Fig. 3) monitors the inspiratory time of the patient's first 3 breaths and creates a template for nebulizing during the first 50% of inspiration during subsequent breaths.

The AeroEclipse is a purely pneumatic device that nebulizes during inspiration (see Fig. 3). The inspiratory effort of the patient engages the nebulizer, producing aerosol during inspiration, and stops nebulizing when patient inspiratory effort ends. A manual override button allows the nebulizer to be engaged manually.

Hospital Versus Home Use

Gas pressure and flow affect particle size distribution and output in pneumatic nebulizers. A nebulizer that produces an MMAD of 2.5 μm when driven by a gas source of 50 psi at 6–10 L/min may produce an MMAD > 8 μm when operated on a home compressor (or ventilator) limited to pressures of 10 psi. Too low a flow can result in negligible output. Consequently, nebulizers used for home care should be matched to the compressor based on data supplied by the manufacturer that the specific combination of equipment will efficiently nebulize the desired medications prescribed for the patient. In Europe, standards have been established that require equipment manufacturers to demonstrate that their nebulizer and compressor combination can nebulize the appropriate fill volume of drug within 10 minutes, deliver $> 50\%$ of the drug in the nebulizer as respirable particles, and identify all medications with which the nebulizer and compressor might reliably meet these two criteria.[9] Clinicians should ascertain that patients are only prescribed systems that have been demonstrated to meet these criteria. PARI and Medic-Aid are examples of manufacturers that have made such validated systems available in the United States.

Other concerns when using disposable nebulizers with compressors at home involve possible degradation of performance of the plastic device over multiple uses. A recent study demonstrated that repeated use did not alter MMAD or output, as long as proper cleaning was performed. Failure to clean the nebulizer properly resulted in degradation of performance of the air-entrainment system, reducing both the output flow and the buildup of electrostatic charge in the device.[11]

The Centers for Disease Control recommend that nebulizers be cleaned and disinfected or rinsed with sterile water between uses, then air dried.[12] Oie and Kamiya, studying microbial contamination of antibiotic aerosol solutions, found that after 7 days, 5 out of 6 solutions were contaminated.[13] The contamination appears to have been caused by storage of multiple dose solutions at room temperature instead of in a refrigerator, and reuse of syringes to measure and dispense the solution. Refrigerating solution and disposing of syringes every 24 hours eliminated bacterial contamination.

Special Medication Delivery Issues for Infants and Children

The airway diameter in children and infants is smaller, the breathing rate is faster, nose breathing filters out large particles and deposits more medication in the upper airway, and mouthpiece administration often cannot be used. Patient cooperation and ability to perform the procedure effectively varies with the patient's age and developmental ability.

For patients who can tolerate a mask, the nebulizer can be fitted to an appropriate aerosol mask. There is no difference in clinical response between mouthpiece and close-fitting mask treatment, so patient compliance and preference should guide selection of the device.[14] If the patient cannot tolerate mask treatment (eg, will not wear the mask closely to the face or gets upset to the point of compromising oxygenation), a commonly employed strategy is use of a "blow-by" technique, in which the practitioner directs the aerosol from the nebulizer toward the patient's nose and mouth. However, there are no published data supporting the use of the "blow-by" technique, and aerosol deposition studies suggest that virtually no drug enters the airway with this technique. The "blow-by" wastes considerable resources, with no evidence of efficacy. It is more efficient to deliver medication by close-fitting mask when the patient is asleep.

Spontaneous breathing results in greater deposition of aerosol from an SVN than does positive pressure breathing (eg, intermittent positive-pressure breathing). Intermittent positive-pressure breathing reduces aerosol deposition by > 30%, compared to spontaneously inhaled aerosols.[15] Normal tidal breathing is the most effective method to administer aerosols to an infant. Mouth breathing enhances medication delivery to the airways in adults, but there are few data on infants who are preferential nose breathers. Crying is a long exhalation preceded by a very short and rapid inhalation. Murakami et al demonstrated that crying completely prevents lower airway deposition of an aerosol medication.[16] Thus, aerosols should never be administered to a crying child.

Large-Volume Nebulizers

A large-volume pneumatic nebulizer (LVN) has a reservoir volume of > 100 mL and can be used to administer an aerosol solution over a prolonged period. Indications for using LVN with a bland solution include humidifying medical gases when the upper airway is bypassed, controlling stridor with a cold aerosol, and inducing sputum. Since nebulizers provide a route of transmission for pathogens, passover humidifiers and heated-wire humidifiers are preferable for humidification.

LVNs work on the same principles as SVNs, with the exception that the residual volume is greater and the effects of evaporation over time are more profound. When using the LVN to administer a solution containing medications such as bronchodilators, the medication becomes increasingly concentrated because of preferential evaporation of the diluent.

LVNs tend to be noisy. Caution should be exercised when using LVNs with incubators or hoods. The American Academy of Pediatrics recommends a sound level < 58 dB to avoid hearing loss in patients in incubators and hoods. Many LVNs are designed to deliver controlled concentrations of oxygen via an entrainment system. Standard entrainment nebulizers may deliver a fraction of delivered oxygen approaching 1.00, but are incapable of providing a fraction of inspired oxygen > 0.40. High flow nebulizers are designed to deliver high oxygen flows, bringing the fraction of inspired oxygen up to 0.60–0.80. Closed dilution and gas injection nebulizers provide high flow access to the nebulizer from two gas sources, allowing gas to mix without compromising the fraction of inspired oxygen (Fig. 4).

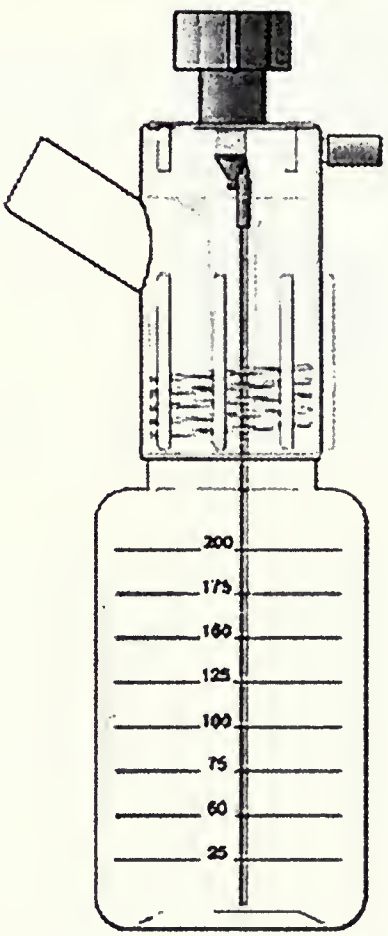


Fig. 4. A closed dilution large-volume nebulizer (Hope Continuous Nebulizer), approved for continuous nebulization of bronchodilators and administration of helium-oxygen mixtures. (Courtesy of B&B Medical Technologies, North Highlands, California.)

Ultrasonic Nebulizers

The USN uses a piezoelectric crystal vibrating at a high frequency to create an aerosol. USNs are capable of a broader range of aerosol output (0.5–7 mL/min) and higher aerosol densities than most conventional jet nebulizers. Particle size is affected by frequency, whereas output is affected by the amplitude of the signal. Particle size is inversely proportional to the frequency of vibrations. Frequency is usually device-specific and is not user-adjustable. For example, the DeVilbiss Portasonic operates at a frequency of 2.25 MHz and produces an MMAD of 2.5 μm, whereas the DeVilbiss Pulmosonic operates at 1.25 MHz and produces particles in the 4–6 μm range. Low flow rates of gas through the nebulizer are associated with higher mist density. Unlike jet nebulizers, the temperature of the solution placed in a USN increases during use. As the temperature increases, the drug concentration can also rise, and some medications, especially proteins, can be denatured by the operating temperature of an ultrasonic nebulizer.[17]

As a USN operates, the aerosol remains in the medication cup/chamber until a flow of gas pushes or pulls the aerosol from the nebulizer. Consequently, if patient exhalation is diverted away from the medication chamber, there

is minimal waste to the atmosphere, and a much greater amount of drug available for inhalation.

Small-volume USNs have been credited with less dead volume than SVNs, theoretically reducing the need for a large quantity of diluent to assure delivery of drugs, although in recent testing in our lab, this does not seem to be the case. The contained portable power source provides convenience and mobility. USNs have been promoted for administration of a wide variety of formulations, ranging from bronchodilators to anti-inflammatory agents and antibiotics, but in general have been shown to be less effective than other delivery devices.[18,19]

The high-density aerosol from USNs has been associated with bronchospasm, increased airway resistance, and irritability in a substantial portion of the population.[20] The structure of the medication may be disrupted by an acoustic power output rated > 50 watts/cm-cm.[21,22] Several ventilator manufacturers are promoting the use of ultrasonic nebulizers for administration of aerosols during mechanical ventilation. The advantage of the USN during mechanical ventilation is the absence of a driving gas flow being added to the circuit, changing ventilator and alarm settings.[23] Disadvantages may include the weight of the USN in the ventilator circuit.

Pressurized Metered-Dose Inhalers

The pMDI is the most commonly prescribed method of aerosol delivery in the world for administering bronchodilators, anticholinergics, anti-inflammatory agents, and steroids. Although some had believed that nebulizers are more effective than pMDIs, there is now considerable evidence that, when properly used, pMDIs are as effective as other nebulizers.[24] Because of their relatively low cost per dose, portability, and multi-dose convenience, pMDIs have become the preferred method for delivering bronchodilators to spontaneously breathing patients and intubated, ventilated patients.[25]

A pMDI contains drug in the form of a micronized powder or solution suspended with a mixture of propellants and a surfactant or a dispersal agent, packaged with a metering valve in a pressurized canister. Metering valve output ranges from 30 μL to 100 μL, and the doses are smaller (between 20 μg and 5 mg of drug per actuation) than the doses delivered by nebulizers. Dispersing agents are present in concentrations equal to or greater than that of the medication, and in some patients they may be associated with coughing and wheezing.[26] The bulk of the spray, up to 80% by weight, is composed of a propellant, commonly a chlorofluorocarbon (CFC) such as FREON. Adverse reactions to CFCs are extremely rare. Because of international agreements to ban CFCs (the Montreal Protocol), new pMDIs are in development that use environmentally benign propellants. The best developed of these new propellants are the hydrofluoroalkanes, such as hydrofluoroalkane 133a.

A pMDI canister contains a pressurized mixture of propellants, surfactants, preservatives, and sometimes flavoring agents, with approximately 1% of the total contents being active drug. This mixture is released from the canister through a metering valve and stem that fits into an actuator boot designed and tested by the manufacturer to work with that specific formulation. Small changes in actuator design can change the characteristics and output of the aerosol from a pMDI.

pMDI actuation into a valved holding chamber decreases impaction losses by reducing the velocity of the aerosol jet,[8] allowing time for evaporation of the propellants and for the particles to age prior to impacting on a surface. The nominal dose of medication with the pMDI is much smaller than with the nebulizer. The quantity of albuterol from a pMDI exiting the actuator nozzle is 100 μg with each actuation or 90 μg from the opening of the actuator boot (this is how pMDI aerosol actuations are characterized in the United States). Thus, a dose of 2–4 actuations (200–400 μg nominal dose) is usually used. In ambulatory patients, 10% deposition may deliver a dose of 20–40 μg for an effective bronchodilator response.

Technique

The ability of the pMDI to reliably deliver medication is technique-dependent. The majority of health professionals who should be teaching pMDI use do not perform the procedure properly (Table 3).[27–29] Good patient instruction can take 10–30 minutes and should include demonstration, practice, and confirmation of patient performance (demonstration placebo units are available for this purpose). Repeated instruction improves performance.[30]

Table 3. Optimal Technique for Use of a pMDI (Bronchodilator Only)

Warm the pMDI canister to hand or body temperature, shake vigorously.
Assemble apparatus, uncap mouthpiece, and make sure there are no loose objects in the device.
Open mouth wide, keep tongue from obstructing the mouthpiece.
Hold the pMDI vertically, with the outlet aimed at mouth.
Place canister outlet between lips, or position the pMDI about 4 cm (two fingers) away from mouth.
Breathe out normally.
As you begin to breathe in slowly (< 0.5 L/s), actuate (fire) the pMDI.
Continue to inhale to total lung capacity.
Hold breath for up to 10 seconds.
Wait 30 seconds between inhalations (actuations).
Disassemble apparatus/recap mouthpiece.

pMDI = pressurized metered-dose inhaler.[27–29]

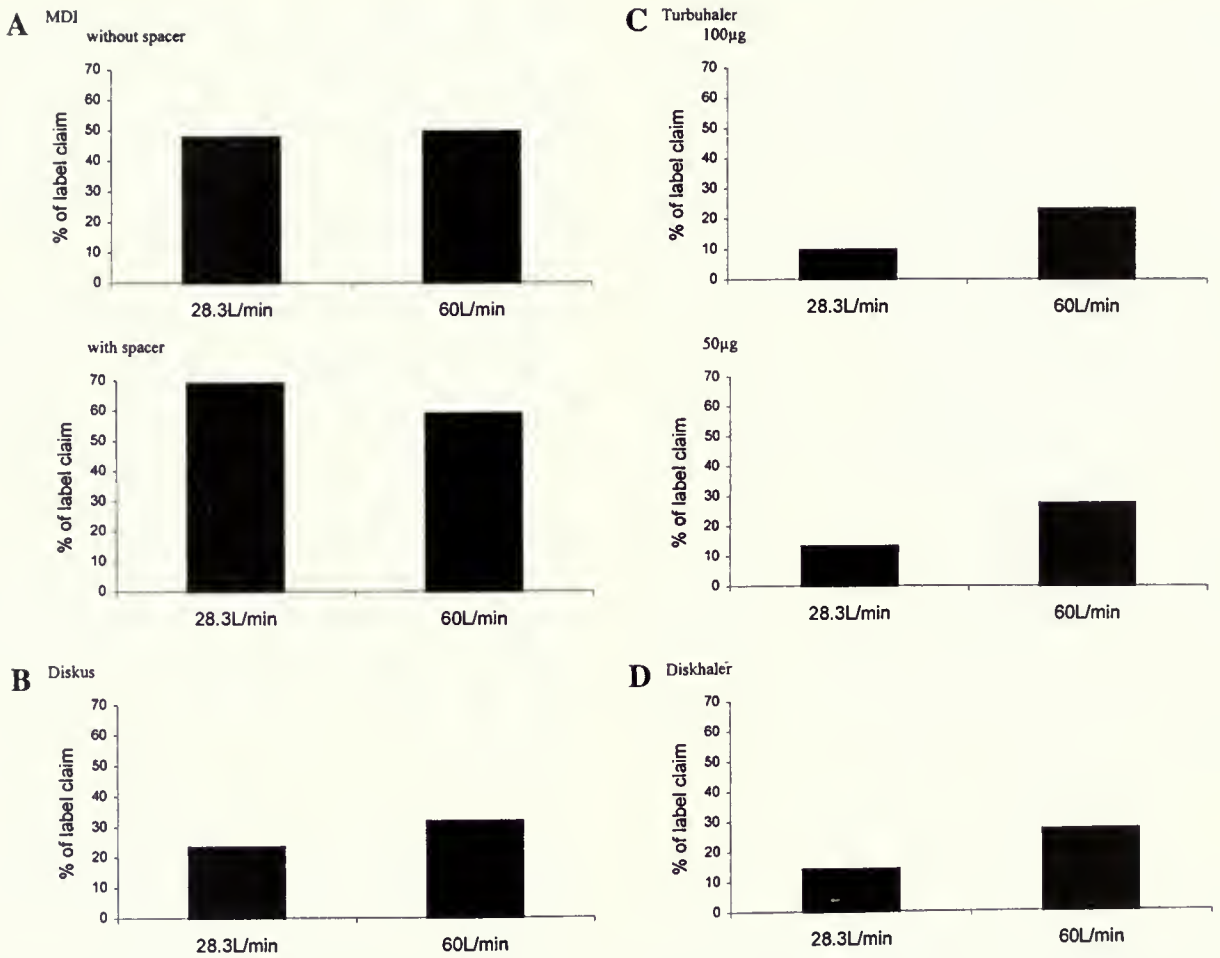


Fig. 5. Comparison of albuterol delivered (percent of label claim) from a variety of metered-dose inhalers and dry powder inhalers when actuated with inspiratory flows of 28.3 L/min and 60 L/min. (From Prime D, Grant AC, Slater AL, Woodhouse RN. A critical comparison of the dose delivery characteristics of four alternative inhalation devices delivering salbutamol: pressurized metered-dose inhaler, Diskus inhaler, Diskhaler inhaler, and Turbuhaler inhaler. J Aerosol Med 1999:12(2);75–84, with permission.)

Infants, young children, elderly patients, and patients in acute distress may not be able to use a pMDI effectively. A "cold FREON effect" can occur when the cold aerosol plume reaches the back of the mouth, causing the patient to stop inhaling.

Problems with home use of pMDI devices include not only poor technique of use but also poor storage. The pMDI should always be stored with the cap on, both to prevent foreign objects from entering the boot and to reduce humidity and microbial contamination. pMDIs should always be discarded when empty, to avoid administering propellant without medication. Although it has been suggested that pMDIs can be tested for drug remaining by floating the canister in water, this technique can be difficult to perform and interpret, and risks contaminating the device. It is easier and more accurate for the patient or parent to note when the medication was started, the number of doses to be taken each day, and the number of doses in the canister, and from this information to calculate a discard date. For example, if there are 200 actuations in a canister (and this information is always indicated on the canister label) and 4 puffs are taken per day, the canister should be discarded 50 days or 7 weeks after the start date. This discard date should be written on the canister label on the day the new canister is started.

Accessory Devices

pMDI accessory devices such as flow-triggered pMDIs, spacers, and valved holding chambers reduce hand-breath coordination problems and high oropharyngeal deposition.

Flow-Triggered Pressurized Metered-Dose Inhaler

Flow-triggering is a mechanism by which a pMDI is actuated by the beginning of inspiration. This reduces the

need for hand-breath coordination.[31] The only flow-triggered pMDI currently available in the United States is the Autohaler. When the inspiratory flow exceeds 30 L/min, a vane moves, causing the canister to be pressed into the actuator, firing the pMDI. Although pirbuterol (a β agonist) is the only medication currently available in this device in the United States, other formulations are available elsewhere. With any flow-triggered device, one concern is whether the patient is able to create adequate inspiratory flow to trigger the device and trigger it early enough in the inspiration that the aerosol reaches the lower airways. Theoretically, small children and patients with acute exacerbations of obstructive lung disease might be unable to use the device effectively, but neither problem appears to exist with the Autohaler.[31]

Spacers and Valved Holding Chambers

Spacers and valved holding chambers are accessory devices that, when properly designed, reduce oropharyngeal deposition of drug, ameliorate the bad taste of some medications, eliminate the cold FREON effect, and in the case of valved holding chambers decrease the need for hand-breath coordination. It is important to differentiate spacers from valved holding chambers. A spacer device is a simple open-ended tube or bag that, with sufficiently large device volume, provides space for the pMDI plume to expand by allowing the CFC propellant to evaporate. To perform this function, a spacer device must have an internal volume of over 100 mL (up to 700 mL), and provide a distance of 10–13 cm between the pMDI nozzle and the first wall or baffle. Smaller inefficient spacers can reduce respiratory dose by 60% and offer no protection against poor coordination between actuation and breathing pattern. Spacers with internal volumes $>$ 100 mL generally provide some protection against early firing of the pMDI, although exhaling immediately following the actuation clears most of the aerosol from the device, wasting the dose.

In addition to the plume-expanding capacity of the spacer, the valved holding chamber incorporates a one-way valve that serves as a baffle that impacts larger aerosol particles and diverts exhaled gas to the atmosphere without clearing any of the aerosol remaining in the chamber. This allows patients with small tidal volume to empty the aerosol from the chamber over the course of 5–6 breaths. A properly designed mask incorporated with a valved holding chamber allows effective pMDI use in patients who cannot use a mouthpiece because of their size, age, coordination, or mental status. With neonates and infants these masks should have minimal dead space and be comfortable to wear.

A valved holding chamber reduces the need to coordinate the breath with actuation, reduces oral deposition (and bad taste) of medication, decreases aerosol MMAD, increases respirable particle mass, improves lower respiratory tract deposition, and significantly improves therapeutic effects. Using a valved holding chamber reduces the taste of medication and the cold FREON effect that can cause children to stop inhaling with pMDI actuation. These devices reduce the pharyngeal dose of aerosol from the pMDI 10–15-fold versus administration without a holding chamber. This decreases total body dose from swallowed medication, which is an important consideration with steroid administration.[32,33]

The high percentage of oropharyngeal drug deposition with steroid pMDIs can increase the risk of oral yeast infections (thrush). Rinsing the mouth after steroid administration can reduce this problem, but most pMDI steroid aerosol impaction occurs deeper in the pharynx, which is not easily rinsed. For this reason, steroid pMDIs should always be used in combination with a valved holding chamber.

When properly used (Table 4), pMDIs with valved holding chambers are at least as reliable as SVNs for aerosol administration in a variety of settings. In a number of randomized, controlled clinical trials in which pMDI with holding chamber was compared to nebulizer therapy in the pediatric emergency setting,[34–36] patients receiving treatment via pMDI with holding chamber or via nebulizer showed comparable improvement over baseline forced expiratory volumes and peak flows, with no significant difference between treatment groups.

Does the pMDI with holding chamber offer a clinical efficacy advantage over a properly-used pMDI alone? As simple as the use of the pMDI, and pMDI with holding chamber appears to the practitioner, instruction with return instruction appears to affect outcome with either device. Cunningham and Crain enrolled 84 emergency department pediatric patients suffering acute asthma attacks to receive inhaled medication via pMDI either with or without a valved holding chamber, preceded by a single brief demonstration of the proper use of a pMDI alone and a pMDI with valved holding chamber. The valved holding chamber group reported significantly faster resolution of wheez-

Table 4. Optimal Technique for Using a pMDI with Valved Holding Chamber

Warm pMDI to hand or body temperature.
Assemble apparatus and make sure there are no objects in device that could be aspirated or obstruct outflow.
Shake canister vigorously and hold canister vertically.
Place holding chamber in mouth (or place mask completely over nose and mouth), encouraging patient to breath through mouth.
Breath normally and actuate at the beginning of inspiration. For small children and infants, continue to breathe through the device for 5 or 6 breaths. Larger breaths with breath-holding may be encouraged in those patients who can cooperate.
Allow 30 seconds between actuations.

pMDI = pressurized metered-dose inhaler.

ing, fewer days of cough, and fewer missed days of school than the group that used pMDIs without holding chambers ($p < 0.01$).[37]

Patients who cannot perform an optimal inspiratory maneuver using a pMDI are seldom able to perform an optimal maneuver using a nebulizer. In either case, when optimal breathing patterns cannot be achieved, it is reasonable to assume aerosol drug delivery will be reduced. In such cases, an alternative to optimizing the inspiratory maneuver is to increase the nominal dose, titrating to achieve the desired clinical outcome.

Care and Cleaning

Particles containing drug settle out and deposit within pMDI spacers and holding chambers, causing a whitish build-up on the inner chamber walls. This residual drug poses no risk to the patient, but may be rinsed out periodically. After washing a chamber or spacer with tap water, it is less effective for the next few puffs, until the static charge in the chamber (which attracts small particles) is once again reduced. Use of regular dish soap reduces or eliminates this static charge.

Accessory devices either use the manufacturer-designed boot that comes with the pMDI, or incorporate a "universal canister adapter" to fire the pMDI canister. Different formulations of pMDI drugs operate at different pressures and have a different size orifice in the boot, which is specifically designed by the manufacturer for use exclusively with that pMDI. Output characteristics of a pMDI will be different when using an adapter with a different size orifice. Therefore, spacers or holding chambers with universal canister adapters should be avoided and only those with a universal boot adapter should be used.

Dry Powder Inhalers

As the technology has evolved, DPIs have gained a greater share of the inhaled drug market, with increasing patient acceptance and product visibility over the past decade. DPIs contain micronized drug particles (< 5 μm MMAD), often aggregated with substantially larger carrier particles (eg, lactose or glucose particles).[38] The carrier particles are larger than the micronized drug, often greater than 30 μm in diameter, and aid the flow of the drug powder from the device by decreasing the cohesive forces in the micronized drug powder. Reducing these cohesive forces prevents the micronized particles from forming nonrespirable clumps. These carriers also add bulk to the powder when the unit dose of a drug is very small. The energy provided by the patient's inhalation strips the drug particles from the carrier. In most DPIs, respirable particles of the drug are released with sufficient inspiratory flow (30–120 L/min).[39,40] With high inspiratory flow, the larger carrier particles impact in the oropharynx while the smaller particles continue to the lower airways. This oropharyngeal impaction of carrier particles gives the patient the sensation of having received a dose.

The internal geometry of a DPI device influences the resistance the device creates to inspiration, and the inspiratory flow required to deaggregate and aerosolize the medication. High-resistance devices (eg, Turbuhaler) require a greater inspiratory flow to deliver a high percentage of the nominal dose. High-resistance DPI provides better drug delivery to the lower respiratory tract than pMDIs,[41,42] but has not been shown to provide better deposition or bronchodilation than low-resistance DPIs. DPIs typically have multiple components that require correct priming to ensure proper dose delivery. Maintenance may include periodic brushing to remove residual powder that accumulates within some DPIs.

Under optimal conditions, most of the drug particles from a DPI are in the respirable range, although the distribution of particle sizes differs substantially among DPIs.[43] High ambient humidity causes clumping of the powder, creating larger, less respirable particles.[44] High ambient humidity tends to increase aerosol particle size and thus reduces drug delivery to the lung. DPIs with sealed or blister pack individual doses that are opened immediately prior to inhalation are less subject to dose reduction from humidity.

Inspiratory Flow

DPIs are critically dependent on inspiratory air flow to generate the aerosol. Thus they should be used with caution (if at all) in the very young or ill child, the weak, the elderly, and those with altered mental status. The magnitude and duration of the patient's inspiratory effort influences aerosol generation from a DPI.[45] Insufficient or low inspiratory flow reduces the dose of the drug emitted from a DPI[46] (Fig. 5).

Active DPI delivery devices that use either an impeller or compressed gas propulsion to disperse the powder are under development and may provide a solution to the flow-dependency of dose delivery.

DPIs are not immune from breath coordination problems. For most DPIs, exhaling into the device blows the powder out of the device, reducing available drug with the next inhalation, and the humidity in the exhaled air reduces aerosol generation.

The technique of using a DPI is different from the technique for a pMDI. Although DPIs are easier to use than pMDIs, up to 25% of patients may use DPIs improperly. As with pMDIs and nebulizers, patients need repeated instruction before they can reliably master DPI technique. Since assessment is necessary to ensure that patients con-

Table 5. Technique for Use of Dry Powder Inhaler

Assemble apparatus.
Load dose: insert and open capsule.
Exhale slowly to FRC.
Seal lips around mouthpiece.
Inhale rapidly (> 60 L/min): breath-hold not necessary.
Repeat process until capsule is empty.
Monitor for adverse reactions.
Assess beneficial effects.

FRC = functional residual capacity.

tinue to use optimal technique, it is recommended that technique be reviewed with each office or clinic visit.[47] In order to train patients correctly, clinicians must learn correct DPI technique (Table 5).

Device Selection and Compliance

With so many devices to choose from, and the range of clinical outcomes associated with their use, it is important that the clinician make selections based on comparative characteristics (Table 6). Other considerations include the following.

Whenever possible, patients should use only one type of aerosol generating device for inhalation therapy. The technique of using each device is different, and repeated instruction is necessary to ensure that the patient uses the device appropriately. Time is money, and each additional device requires more time to teach. More importantly, the use of different devices for inhalation can be confusing for patients and may decrease their compliance with therapy.

At present, DPIs can be considered as alternatives to pMDIs for patients who can generate inspiratory flows > 30–60 L/min and who are unable to use pMDIs effectively. DPIs are recommended for patients with stable asthma and chronic obstructive pulmonary disease, but not for patients with acute bronchoconstriction, or children < 6 years old. Therefore, one drawback of DPIs is that they do not substitute for pMDIs in all clinical situations. Moreover, dose adjustment may be needed when a drug is administered via DPI instead of via pMDI. Deciding on the appropriate dose of inhaled corticosteroids may be a particularly vexing problem, since it is difficult to determine bioequivalence with these agents. Further research is needed to determine equivalent dosages when both the drug and the device used for inhalation therapy are altered.

To improve compliance, aerosol therapy should be administered along with some easily remembered activity of daily living. For twice daily administration, medications can be kept with the toothbrush and inhaled just before brushing teeth. This will also reduce aerosol corticosteroid deposition in the oropharynx. It is always best to avoid the regular use of medication at school, because the inconvenience can significantly reduce compliance and may be an embarrassment to some children. However, the availability of rescue medication at school (or daycare or other caretaker's home) must be assured. It helps to prepare written guidelines for medication use, but these guidelines must be distributed to all places the child stays: home, school, and, in the case of divorce or separation, at the residences of both parents.

It is helpful, at least initially, to keep a diary of medication use. Lack of response to inhaled asthma medication

Table 6. Comparison of Characteristics to Guide Device Selection

	MDI with holding chamber	SVN	DPI	USN	MDI alone
Flow independent	+++	+++	−	+++	−
Volume independent	+++	+++	−−	+++	−
Coordination independent	+++	+++	+	++	−
Low oral deposition	+++	−	−	−	−
Easy to use	+++	+++	+++	++	++
Portable	+++	+	+++	+	+++
Quick to administer	+++	+	+++	+	+++
Low cost	++	−	++	−−−	+++
Low infection risk	+++	−−−	+++	−−−	+++
Effective with					
Severe asthma	+++	+++	+	+	+
Small children	+++	+++	−	++	−
Ventilators	++++	++	−−	+++	−
Unusual medication	−−	+++	−−	+	−−

+ = positive characteristic. − = negative characteristic. MDI = metered-dose inhaler. SVN = small-volume nebulizer. DPI = dry powder inhaler. USN = ultrasonic nebulizer.

can be related to a number of factors, including incorrect technique of inhalation, inadvertently inhaling from empty canisters, not taking preventer medications as prescribed, change in the child's environment, and perhaps to misdiagnosis. For example, a child with an aspirated foreign body, gastroesophageal reflux disease, or psychogenic wheeze will have a poor response to asthma therapy, and an infant with tracheomalacia or bronchopulmonary dysplasia may even become much worse after inhaling a bronchodilator aerosol because of increased dynamic airway collapse.[48]

Summary

Therapeutic aerosols are generated by pneumatic jet nebulizers, ultrasonic nebulizers, pressurized metered-dose inhalers, and dry powder inhalers. Some of the drug preparations used in these devices are formulated to work with specific devices. Although design improvements in aerosol devices have led to improved lung deposition, decreased oropharyngeal deposition, decreased waste of drug, greater ease of use, and lower environmental impact, optimizing the use of aerosol devices requires patient and caregiver instruction, in combination with proper device use and maintenance. Optimizing aerosol delivery requires knowledge of a number of technical details, and caregivers should stay abreast of the continuing advancement of technologies and techniques associated with aerosol delivery, especially in light of emerging devices and formulations.

REFERENCES

1. Hess D, Fisher D, Williams P, Pooler S, Kacmarek RM. Medication nebulizer performance: effects of diluent volume, nebulizer flow, and nebulizer brand. Chest 1996;110(2):498–505.
2. Hadfield JW, Windebank WJ, Bateman JRM. Is driving gas flow rate clinically important for nebulizer therapy? Br J Dis Chest 1986; 80(1):50–54.
3. Douglas JG, Leslie MJ, Crompton GK, Grant IWB. A comparative study of two doses of salbutomol nebulized at 4 and 8 litres per minute in patients with chronic asthma. Br J Dis Chest 1986;80(1): 55–58.
4. Hess DR, Acosta FL, Ritz RH, Kacmarek RM, Camargo CA Jr. The effect of heliox on nebulizer function using a beta-agonist bronchodilator. Chest 1999;115(1):184–189.
5. Fink J, Dhand R, Fahey P, Tobin MJ. Heliox increased delivery of albuterol during mechanical ventilation: an in-vitro model. Am J Respir Crit Care Med 1997;155:A268.
6. Malone RA, Hollie MC, Glynn-Barnhart A, Nelson HS. Optimal duration of nebulized albuterol therapy. Chest 1993;104(4):1114–1118.
7. Thomas SH, Langford JA, George RD, Geddes DM. Improving the efficiency of drug administration with jet nebulisers (letter). Lancet 1988;1(8577):126.
8. Fink JB, Dhand R. Aerosol therapy. In: Fink JB, Hunt G, editors. Clinical practice in respiratory care. Philadelphia: Lippincott Raven; 1998.
9. The Nebuliser Project Group of the British Thoracic Society Standards of Care Committee: Current best practice for nebuliser treatment. Thorax 1997;52(Suppl 2):S4–S16.
10. Newnham DM, Lipworth BJ. Nebulizer performance, pharmokinetics, airways and systemic effects of salbutamol given via a novel nebuliser delivery system ("Ventstream"). Thorax 1994;49(8):762–770.
11. Standaert TA, Morlin GL, Williams-Warren J, Joy P, Pepe MS, Weber A, Ramsey BW. Effects of repetitive use and cleaning techniques of disposable jet nebulizers on aerosol generation. Chest 1998; 114(2):577–586.
12. Centers for Disease Control and Prevention: Guidelines for prevention of nosocomial pneumonia. Part 1. Issues on prevention of nosocomial pneumonia. 1994.
13. Oie S, Kamiya A. Bacterial contamination of aerosol solutions containing antibiotics. Microbios. 1995;82(331):109–113.
14. Lowenthal D, Kattan M. Facemasks versus mouthpieces for aerosol treatment of asthmatic children. Pediatric Pulmonol 1992;14(3):192–196.
15. Dolovich MB, Killian D, Wolff RK, Obminski G, Newhouse MT. Pulmonary aerosol deposition in chronic bronchitis: intermittent positive pressure breathing versus quiet breathing. Am Rev Respir Dis 1977;115(3):397–402.
16. Murakami G, Igarashi T, Adachi Y, Matsuno M, Adachi Y, Sawai M, et al. Measurement of bronchial hyperreactivity in infants and preschool children using a new method. Ann Allergy 1990;64(4): 383–387
17. Phillips GD, Millard FJL. The therapeutic use of ultrasonic nebulizers in acute asthma. Respir Med 1994;88(5):387–389.
18. Yuksel B, Greenough A. Comparison of the effects on lung function of two methods of bronchodilator administration, Respir Med 1994: 88(3):229–233.
19. Nakanishi AK, Lamb BM, Foster C, Rubin BK. Ultrasonic nebulization of albuterol is no more effective than jet nebulization for the treatment of acute asthma in children. Chest 1997;111(6):1505–1508.
20. Lewis RA, Ellis CJ, Fleming JS, Balachandran W. Ultrasonic and jet nebulizers: differences in the physical properties and fractional deposition on the airway responses to nebulized water and saline aerosols (abstract). Thorax 1984;39:712.
21. Doershuk CF, Matthews LW, Gillespie CT, Lough MD, Spector S. Evaluation of jet-type and ultrasonic nebulizers in mist tent therapy for cystic fibrosis. Pediatrics 1968;41(4):723–732.
22. Boucher RM, Kreuter J. The fundamentals of the ultrasonic atomization of medicated solutions. Ann Allergy 1968;26(1):591–600.
23. Thomas SH, O'Doherty MJ, Page CJ, Treacher DF, Nunan TO. Delivery of ultrasonic nebulized aerosols to a lung model during mechanical ventilation. Am Rev Respir Dis 1993;148(4 Pt 1):872–877.
24. Lin YZ, Hsieh KH. Metered dose inhaler and nebulizer in acute asthma, Arch Dis Child 1995;72:214–218.
25. AARC Clinical Practice Guideline. Selection of aerosol delivery device. American Association for Respiratory Care. Respir Care 1992; 37(8):891–897.
26. Newhouse MT, Dolovich M. Aerosol therapy in children. basic mechanisms of pediatric respiratory disease: cellular and integrative. New York: BC Decker; 1991.
27. Larsen JS, Hahn M, Ekholm B, Wick KA. Evaluation of conventional press-and-breathe metered-dose inhaler technique in 501 patients. J Asthma 1994;31(3):193–199.
28. Guidry GG, Brown WD, Stogner SW, George RB. Incorrect use of metered dose inhalers by medical personnel. Chest 1992;101(1):31–33.

29. Newman SP, Pavia D, Clarke SW. Simple instructions for using pressurized aerosol bronchodilators J R Soc Med 1980;73(11):776–779.
30. De Blaquiere P, Christensen DB, Carter WB, Martin TR. Use and misuse of metered-dose inhalers by patients with chronic lung disease: a controlled, randomized trial of two instruction methods. Am Rev Respir Dis 1989;140(4):910–916.
31. Hampson NB, Mueller MP. Reduction in patient timing errors using a breath-activated metered dose inhaler. Chest 1994;106(2):462–465.
32. Salzman GA, Pyszczynski DR. Oropharyngeal candidiasis in patients treated with beclomethasone dipropionate delivered by metered-dose inhaler alone and with Aerochamber. J Allergy Clin Immunol 1988;81(2):424–428.
33. Toogood JH, Baskerville J, Jennings B, Lefcoe NM, Johansson SA. Use of spacers to facilitate inhaled corticosteroid treatment of asthma. Am Rev Respir Dis 1984;129(5):723–729.
34. Rubin BK. Pressurized metered-dose inhalers and holding chambers for inhaled glucocorticoid therapy in childhood asthma (letter). J Allergy Clin Immunol 1999;103(6):1224–1225.
35. Closa RM, Ceballos JM, Gomez-Papi A, Galiana AS, Gutierrez C, Marti-Henneber C. Efficacy of bronchodilators administered by nebulizers versus spacer deivces in infants with acute wheezing. Pediatr Pulmonol 1998;26(5):344–348.
36. Williams JR, Bothner JP, Swanton RD. Delivery of albuterol in a pediatric emergency department. Pediatr Emerg Care 1996;12(4):263–267.
37. Cunningham SJ, Crain EF. Reduction of morbidity in asthmatic children given a spacer device. Chest 1994;106(3):753–757.
38. Ganderton D. The generation of respirable clouds from coarse powder aggregates. J Biopharm Sci 1992;3:101–105.
39. Engel T, Heinig JH, Madsen F, Nikander K. Peak inspiratory flow and inspiratory vital capacity of patients with asthma measured with and without a new dry-powder inhaler device (Turbuhaler). Eur Respir J 1990;3(9):1037–1041.
40. Pederson S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. Arch Dis Child 1990;65(3):308–310.
41. Thorsson L, Edsbacker S, Conradson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler (pMDI). Eur Respir J 1994;7(10):1839–1844.
42. Svartengren K, Lindestad PA, Svartengren M, Philipson K, Bylin G, Camner P. Added external resistance reduces oropharyngeal deposition and increases lung deposition of aerosol particles in asthmatics. Am J Respir Crit Care Med 1995;152(1):32–37.
43. Hill LS, Slater AL. A comparison of the performance of two modern multidose dry powder asthma inhalers. Respir Med 1998;92(1):105–110.
44. Rajkumari NJ, Byron PR, Dalby RN. Testing of dry powder aerosol formulations in different environmental conditions. Int J Pharm 1995;113:123–130.
45. Timsina MP, Martin GP, Van der Kolk H, Tushulzen E, Enthoben R. The effect of inhalation flow on the performance of a dry powder inhalation system. Int J Pharm 1992;81:199–203.
46. Hindle M, Byron PR. Dose emissions from marketed dry powder inhalers. Int J Pharm 1995;116:169–177.
47. Kesten S, Elias M, Cartier A, Chapman KR. Patient handling of a multidose dry powder inhalation device for albuterol. Chest 1994;105(4):1077–1081.
48. Rubin BK. Tracheomalacia as a cause of respiratory compromise in infants. Clin Pulm Med 1999;6:195–197.

Books, Films, Tapes, & Software

Anticholinergic Agents in the Upper and Lower Airways. Sheldon L Spector, Editor. (Lung Biology in Health and Disease, Volume 134, Claude Lenfant, Executive Editor.) New York/Basel: Marcel Dekker. 1999. Hardcover, illustrated, 212 pages, $135.

Anticholinergic Agents in the Upper and Lower Airways is Volume 134 in the excellent and comprehensive series, Lung Biology in Health and Disease. This 212-page multiple-author (n = 10) hardcover book covers the pharmacology, physiology, and clinical usefulness of topical anticholinergic (antimuscarinic) agents in the nose and lungs. Since there is currently essentially only one topical pharmacologic agent in this category of muscarinic antagonists, this volume deals primarily with the drug ipratropium bromide (Atrovent, made by Boehringer Ingelheim).

The book is divided into 10 chapters in 3 sections. The first section is a basic science section encompassing two chapters: one on muscarinic physiology and one on muscarinic receptors. These two chapters contain (perhaps necessarily) substantial overlap. This is the only major overlap between chapters in the book. The basic physiology, including muscarinic receptors, is reviewed comprehensively and in great depth.

The second section, "Applied Clinical Research," reviews the clinical value of antimuscarinic agents in both nasal and airway disease. The 6 chapters in this section include an in-depth review of the bronchodilator properties of anticholinergics, particularly ipratropium bromide, followed by chapters on the use of ipratropium in chronic air flow limitation (or chronic obstructive pulmonary disease), acute severe asthma, perennial rhinitis, and infective rhinitis (ie, the common cold). Finally, there is a chapter on an exciting new long-acting anticholinergic agent called tiotropium bromide (made by Boehringer Ingelheim). I found these 6 chapters to be up to date and a thorough comprehensive review of the place of these agents in current treatment guidelines. The conclusions are presented in a fair and unbiased way. The chapter on infective rhinitis by Dr Spector is particularly interesting, presenting a detailed review of the (somewhat limited in terms of efficacy) treatment options in the management of the common cold. This is particularly valuable, since this extremely common affliction receives very limited scientific press.

The final section, "Topics of Special Interest," includes two chapters. The first is a very entertaining review of the many thousands of years of history of the use of anticholinergic agents, both for their psychotropic and bronchodilator effects. The second chapter is a somewhat theoretical approach to reviewing interactions of viral infections with muscarinic receptors, in an attempt to explain in whole or in part viral-induced exacerbations of asthma.

This is an excellent reference book on the current state of the art of topical anticholinergic (antimuscarinic) agents in the management of rhinitis and lower airway disease. Though appropriate for any discipline interested in respiratory health, I would regard this primarily as a reference text that would be of value to physicians. The diseases dealt with (eg, asthma, chronic air flow limitation, rhinitis) are common and seen by many medical specialists. Practitioners in respiratory medicine, allergy, internal medicine, pediatrics, and family practice would all find useful information in reading or referring to this book.

I found all the chapters to be comprehensive, up-to-date reviews, with data presented in an accurate, fair fashion. The chapters I enjoyed the most were the one on the common cold and the one on the history of muscarinic agents, although these are the two chapters with the most limited clinical relevance to current treatment.

By way of minor criticism, I think that the order of presentations could have been improved. This is a minor criticism in a book with only 10 chapters. It would seem logical (to me) to have introduced the topic with the historical chapter. It would then be appropriate to follow this with the basic physiology. The clinical section would more logically flow if all the chapters on lung (airway) disease were lumped together (ie, bronchodilation, chronic air flow limitation/chronic obstructive pulmonary disease, tiotropium bromide, asthma, and virus/muscarinic receptors).

In summary, this is a valuable review and reference book on topical antimuscarinic pharmacologic agents in the treatment of upper and lower airways disease. It is a valuable reference for clinicians dealing with these common disorders.

Donald W Cockcroft MD
Department of Medicine
Division of Respiratory Medicine
Royal University Hospital
University of Saskatchewan
Saskatoon, Saskatchewan, Canada

Exercise-Induced Asthma. ER McFadden Jr, Editor. (Lung Biology in Health and Disease, Volume 130, Claude Lenfant, Executive Editor.) New York/Basel: Marcel Dekker. 1999. Hardcover, illustrated, 388 pages, $175.

This is the 130th volume of the Lung Biology in Health and Disease series under the directorship of Dr Claude Lenfant at the National Heart Lung and Blood Institute of the National Institutes of Health. Dr McFadden has assembled an expert group of authors to write the "definitive" (like so many of the other volumes in this series) text on exercise-induced asthma (EIA). The intended audience is physicians, respiratory physiologists, and therapists who care for adults and children with asthma. As Dr McFadden discusses in his preface, "Of all the multiple triggers that induce acute asthma, exercise is the most ubiquitous and one of the few that have the potential to trouble all patients with asthma and to interfere with their ability to function in daily life." Like many things in medicine, despite the fact that potentially everyone with asthma can exhibit EIA, it goes unrecognized too often, and the pathogenesis, until recently, has remained elusive.

The book opens with a nicely written historical perspective of EIA. The second chapter provides an in-depth introduction to the clinical and physiologic features of EIA. This chapter is quite comprehensive and nicely sets the stage for many of the subsequent chapters, which dissect the various aspects of this condition in detail. The following several chapters are entirely devoted to the physiology and immunology involved in the pathogenesis of EIA, with chapters on "Respiratory Heat Exchange and Exercise-Induced Asthma" (Chapter 3), "Airway

Drying and Exercise-Induced Asthma" (Chapter 4), "Exercise-Induced Asthma as a Vascular Phenomenon" (Chapter 5), "Inflammatory Mediators in Exercise-Induced Asthma" (Chapter 6), and the "Role of 5-Lipoxygenase Metabolites of Arachidonic Acid in Exercise-Induced Asthma" (Chapter 7).

The third section addresses the clinical manifestations, evaluation, and treatment of this condition, with superbly written chapters on "Exercise Refractoriness" (Chapter 8), "Late Reactions and Exercise-Induced Asthma" (Chapter 9), "Exercise, Hyperventilation, and Nonisotonic Aerosols in Exercise-Induced Asthma" (Chapter 10), "Exercise Testing in Adults and Children" (Chapter 11), "Air Pollution and Exercise-Induced Bronchoconstriction" (Chapter 12), and "Prevention and Treatment of Exercise-Induced Asthma" (Chapter 13). The last chapter of the book is devoted to a discussion of experimental models of EIA.

This book is necessary for all with an interest in asthma. From a clinician's perspective, the first and third sections are more than sufficient to gain a better understanding of the clinical manifestations, prevention, and treatment of EIA. The middle chapters will be invaluable to respiratory physiologists, respiratory therapists, and researchers interested in the complexities involved in the pathogenesis of this condition. Important points the book makes include the finding that all asthmatics under the right circumstances can have EIA. Of importance, EIA usually does not occur during exercise. Rather, EIA begins shortly after stopping exercise, with the most pronounced loss of lung function occurring 5–15 minutes after exercise. The precise mechanism remains elusive, but EIA is thought to be a "thermal phenomenon" in which airway cooling and rewarming as a consequence of exercise results in bronchial narrowing.

An intriguing and little known aspect of EIA is the phenomenon of exercise refractoriness, which is the topic of the chapter by Dr O'Byrne, who describes the long known observation that, following an episode of EIA, an asthmatic is less likely to have another episode with subsequent exercise for up to 4 hours. Some asthmatics can exploit this phenomenon by producing EIA in their warm-up prior to their athletic endeavor. Last, certain forms of exercise are more likely to cause EIA than others. Even accounting for differences in air temperature and humidity, swimming appears to be the least likely to induce EIA, whereas running is most likely to induce it. Thus, in some asthmatics with EIA refractory to medications such as inhaled β agonists or cromolyn/nedocromil, a switch from long distance running to swimming may be the best change of exercise. This field has come a long way in a short period. Asthmatics from a generation ago were not allowed to participate in sporting events. At that time, we did not understand EIA, nor did we have an effective treatment. Today, even the most severely asthmatic person can participate in athletic events.

Joseph D Spahn MD
Department of Pediatrics
National Jewish Medical and
Research Center
University of Colorado
Health Sciences Center
Denver, Colorado

Oxford Textbook of Critical Care. Andrew R Webb, Marc J Shapiro, Mervyn Singer, and Peter M Suter, Editors. Oxford: Oxford University Press. 1999. Hardcover, 1,384 pages plus index, $198.50.

Like many intensivists, I have been searching for the perfect critical care reference book. The textbook would need to be broad in its scope but detailed in terms of pathophysiology, therapeutics, and practice recommendations. There are plenty of textbooks available, but they all fall short of providing thorough coverage of every topic. Frustrated with the shortcomings of most books, I have largely turned to multiple specialized textbooks such as Martin Tobin's excellent companion books *Principles and Practice of Mechanical Ventilation* and *Principles and Practice of Intensive Care Monitoring*, Dantzker and Scharfs's *Cardiopulmonary Critical Care*, and Goldfrank's *Toxicologic Emergencies*. Needless to say, I was not optimistic that the **Oxford Textbook of Critical Care** would be the perfect critical care reference. However, this textbook impressed me. The editors wanted to provide a patient-oriented reference that could aid decision-making at the bedside and provide information based on sound pathophysiologic principles. Surprisingly, they acknowledged at the outset that a detailed discussion of every critical care topic is an impossible task. Thus, they decided to provide a broad list of topics presented in an efficient monograph form. The other unique feature in this book is that the topics are centered around specific problems or symptoms in critical care rather than organized by system. The approach and ultimate result is very refreshing.

The book itself is fairly sturdy, in a gray, green, and silver cover. The cover showed signs of wear and tear quite quickly, and the green dye would occasionally rub off on my hands, but the binding held well. The print and paper are of good quality and durability. The best aesthetic feature of the book is the two attached ribbons that serve as page markers, a standard in books from the Oxford University Press. The 450 international authors are leaders in their respective fields, and the editors should be commended for organizing such a diverse group of writers. A thorough index makes looking up subjects straightforward. The book was designed with CD-ROM technology in mind, and the editors claim that the CD version is organized to allow efficient searching and display of relevant material.

As mentioned earlier, the organization is quite unique. Chapters are grouped by system (eg, respiratory) or general problem (eg, nutrition, poisoning). The first chapter in each section is generally a physiology review or overview chapter, followed by specific chapters that focus on specific clinical problems or symptoms encountered in the care of critically ill patients. For example, the section on the neurological system starts with a brief overview of normal physiology. This is followed by a chapter on the unconscious patient, which is divided into subchapters covering pathophysiology, causes, and management. The next chapter deals with seizures, and others deal with weakness, meningitis, encephalitis, sleep disturbance, pain, and agitation. The section on poisoning starts with a chapter on principles of management, followed by chapters on 14 common poisonings encountered in the intensive care unit. The list of topics covered is indeed extensive and complete. Every major system is covered (respiratory, cardiovascular, gastrointestinal/hepatic, renal, neurological, endocrine/metabolic, hematological), and the problem-oriented sections cover a diverse array of topics, including resuscitation, nutrition, poisoning, trauma/burns, obstetric, infection/inflammation, perioperative care, monitoring, critical care organization, pharmacotherapeutics, and therapeutic equipment/techniques.

Overall, the chapters are concise, well organized, and well written. The beginning of each subchapter contains a series of help-

ful "key messages" that summarize the points of the chapter. The brevity of each chapter precludes a detailed discussion of each topic. This is perfect when the reader needs a concise overview of a problem, but falls short if one needs an extensive explanation, especially when the topic is controversial or complicated. For example, the section on multi-organ dysfunction utilized only two paragraphs to discuss gut mucosal integrity and bacterial translocation. The paragraphs are well written and concise and they would be perfect for a resident reviewing the topic before morning rounds. However, the discussion is insufficient for a fellow trying to study for the boards or preparing a lecture on the subject. A complete set of references would mitigate this problem, but unfortunately the editors decided to provide only a few references for each chapter, and major points are only occasionally referenced.

The talent required to write a concise review of a topic is considerable, and some of the sections fall short. For example, the section on nutrition is too brief to say anything meaningful and leaves the reader without a clear understanding of the basis for the recommended guidelines. Other sections, such as the neurologic and renal sections, are very well done. The respiratory section is quite extensive and contains excellent discussions of atelectasis, sputum retention, hemoptysis, pneumothorax, bronchospasm, and failure to wean. The section on the breathless patient was unique and also well presented. In many of the sections a few clinical case scenarios would be helpful to solidify the concepts touched on in the chapters. The chapters on normal physiology are useful only as a tool to familiarize the reader with a few concepts. The chapters are only 3–10 pages and often contain brief overviews of complicated topics (eg, multiple inert gas elimination technique or MIGET) that would be difficult to understand even if 10 times the space were used. The editing is excellent and there are very few typographical errors or omissions.

The book really shines as a tool to address specific problems encountered in the intensive care unit. I could envision a house officer encountering a patient with oliguria and consulting the textbook or CD-ROM to get a concise summary of the subject, the approach to the oliguric patient, and various diagnostic and therapeutic considerations. Similarly, a nurse or respiratory therapist could use the book to review an unfamiliar topic encountered in the routine care of a critically ill patient, such as the use of a mixed venous saturation. The book cannot be used to fully understand a topic, and thus will often require supplementation with original articles and more specialized texts. The chapters, however, can be used as a starting point or as an intellectual aid in organizing a topic before further research.

I applaud the editors on their approach to critical care, and find the organization and writing in this textbook refreshing. I would recommend it as the standard reference in critical care libraries at teaching institutions and in critical care nursing or respiratory therapy departments. Primary care physicians, residents, nurses, and respiratory therapists would greatly benefit from its concise and organized monographs on the diverse problems encountered in the intensive care unit. Intensivists and fellows in critical care will want something more detailed, but may want to add this book to their personal library if they don't have access to it otherwise. Unfortunately, if a patient has a problem that an intensivist is actively managing, a more thorough knowledge of the subject is needed than is provided in this book. The chapters could be used by specialists as a starting point for research on an unfamiliar topic. The addition of specific case scenarios and expansion of the references at the end of each chapter would increase the utility of this textbook and help compensate for the brevity of many sections. Ultimately, the strengths of this textbook are also its weaknesses. Although I will probably always start with the **Oxford Textbook of Critical Care**, I will continue to use my specialized textbooks to thoroughly understand my patients' problems. Critical care is an evolving and expansive subspecialty that involves treating the sickest and most complicated patients from medicine, surgery, neurology, and other departments. It would be foolish to think that this discipline could be fully contained between only two covers. By acknowledging this and using a fresh, problem-based approach, the editors have created a very useful reference.

Benjamin D Medoff MD
Pulmonary and Critical Care Unit
Department of Medicine
Massachusetts General Hospital
Boston, Massachusetts

Atlas of Sleep Medicine in Infants and Children. Stephen H Sheldon DO, Susan Riter MD, Mark Detrojan R PSG T. Armonk, New York: Futura Publishing. 1999. Hardcover, illustrated, 278 pages, $150.

This book presents 72 segments of children's polysomnograms, with brief discussions of the tracings and, frequently, brief clinical presentation of the patients. The book is described "...as a beginning. It is offered to assist practitioners...in caring for children who suffer during their hours of sleep."

This book would be most useful for physicians and polysomnography technologists who already possess some expertise in sleep medicine. It is divided into 5 sections:

I. Standard and Recommended Recording Montage

II. Pneumography, Home Monitoring and Event Recording

III. Recording Artifacts

IV. The Normal Polysomnogram in Infants and Children

V. The Abnormal Polysomnogram in Infants and Children

The material is well selected and organized but would be applicable to a wider audience with more detail and discussion of the basics. A diagram showing electrode placement on the head would be helpful for practitioners who are most familiar with a simple respiratory-oriented montage. Figure 1 describes the standard polysomnogram montage, consisting of 4 electroencephalogram leads. This is the last time this montage is seen in the book; clearly, the authors prefer a more detailed montage. Some discussion of the differences between the "standard" and their preferred 7-lead montage would be helpful, particularly describing the relative merits and deficiencies of the two choices.

A discussion of the different types of sensors would be helpful, particularly respiratory inductance plethysmography versus strain gauges or impedance measurements, thermistors versus measurement of exhaled CO_2 or pressure transducers, and the relative merits of analog versus digital recording.

The section on pneumography shows well the differences between pneumography and polysomnography, and provides good examples and discussion of home event recordings. The case descriptions are well detailed. However, the authors should be careful about what is considered "pathologic," since the clinical importance of cardio-

respiratory events, particularly central apneas, is not clear.

The section on artifacts has good examples and discussions of electroencephalography and patient artifacts. Artifacts of the respiratory sensors, such as respiratory inductive plethysmography belts sliding together producing the illusion of synchronous breathing during obstructed events, would be helpful.

The section on normal polysomnography also shows good, detailed examples. The captions would be more helpful if they were more specific, describing the finding exhibited rather than simply "normal sleep in a 3-year-old child."

The section on abnormal polysomnography has an excellent presentation and discussion of nonrespiratory sleep disorders. Providing definitions of terms such as "hypersynchronous theta" and "hypsarrhythmia," which might not be familiar to those with a primarily respiratory background, would broaden the book's utility. The examples of respiratory disorders could have been better selected to represent convention. For example, Figure 40 shows expiration on the ETCO2 channel in the downward direction, but expiration is more commonly portrayed in the upward direction. There is a persistent problem throughout these examples of the phase of the chest wall and abdomen signals. Figure 41A shows the chest wall and abdomen to be out of phase, consistent with obstructed efforts, but the caption describes respirations as "regular," suggesting this may be an artifact. Similarly, in Figure 42, which purports to describe obstructive sleep apnea, the chest wall and abdominal efforts are in phase. Figure 51A shows the chest wall and abdomen to be out of phase in a child with a tracheostomy. If these recordings of respiratory effort truly depict what the child was doing, some comment in the caption would be warranted. If they represent (as I suspect) artifact, better examples should have been selected.

The book is well presented and easy to read, and the reproduction of the polysomnography tracings is excellent. This book would be quite useful as a reference for those involved in polysomnography who already have some expertise, particularly with recordings of respiratory events. A bit more detail in the discussions would make this good and useful volume superb.

Lee J Brooks MD
Department of Pediatrics
Robert Wood Johnson Medical School
Pediatric Pulmonary Division
Family Sleep Center
The Children's Regional Hospital
at Cooper
Camden, New Jersey

LifeMasters Online
(reviewed April 6–24, 2000)

LifeMasters Online (http://www.lifemastersonline.com) provides an interesting glimpse into a possible future health care delivery system. Patients would monitor themselves at home and upload data over the Internet to a central database. The database would alert the patient and appropriate health care provider of any important changes. Changes in treatment would be discussed and implemented before a condition worsened enough to require an office or urgent-care visit. Patient training would be customized for the patient's condition and level of comprehension. Prevention would help improve health care utilization.

LifeMasters Online has this goal squarely in sight and sets out to provide patient education, health management, and support. They succeed, to a great extent, on all three. They are stepping onto a playing field where the rules are not yet solidified; therefore, there is no real measure by which to determine their success.

Foremost in the discussion of any online medical information is the issue of privacy. The privacy policy should be the first stop on any Web site. The **LifeMasters Online** policy states that "personal and medical information" will not be released without consent, but it may be released if "required to disclose such information by law." They continue by stating that "other information" the patient submits is nonconfidential and may be used as they see fit. Users of the site should be aware of this relatively open policy.

Much of the material on the Web site is unavailable unless you register. Registration involves entering your e-mail address and choosing a password. Additional personal information can then be entered, along with insurance and medical data.

The first section of the Web site provides patient education for the following chronic diseases: asthma, chronic obstructive pulmonary disease, congestive heart failure, coronary artery disease, diabetes, and hypertension.

Each of the topics has enough information for a patient to understand basic problems and treatment. There are many links to terms that may need additional explanation, such as pursed-lip and diaphragmatic breathing. Each topic also provides a list of medication classes used for treatment and allows the patient to get more detailed information if they wish. For example, in the asthma section, bronchodilators are divided into quick-relief and long-term categories. Quick-relief is further defined as a β-2 agonist, along with common trade and generic names. The patient may read as much or as little detail as he or she desires.

The information provided is useful as a patient teaching aid, although most health care providers already have similar written information to give to patients. The advantage with **LifeMasters Online** is that the patient can "customize" the teaching to provide just the information needed or desired. One complaint is that no source is given for the information. Though most patients would not look up medical citations, it would be useful to practitioners who are asked by patients why the Web site has different information than what they have been told previously.

The second part of the Web site is called Health Management. It starts with a simple health risk assessment that points the patient to other sections, as needed. Additional education is provided for diet and nutrition. A log can be maintained for up to 60 days tracking blood pressure, weight, smoking, and peak flow. The values are automatically graphed and may be printed out for review with health care providers. Blood pressure data are checked to see if values fall outside the American Heart Association recommendations and a red/yellow/green zone is calculated for peak flow. A preventive care plan can be generated using patient-supplied information.

In order to test the health management portion, a hypothetical hypertensive asthmatic patient was created and data were entered over a 2-week period. Blood pressure information and peak expiratory flow were entered over the review period. High blood pressure was correctly flagged and a notice was displayed for the patient. There is a slight bug in the software; if systolic and diastolic pressures are switched around, there is no warning. Peak flows were entered that fell into the calculated red zone ($<$ 50% of personal best peak expiratory flow), but no warning was given. A medication record keeps track of doses taken and remaining in a prescription and can connect the patient to **planetrx.com** or **drugstore.com** for refills. There is no indication of sponsorship or other agreement with the latter two retail services.

The preventive care plan suggested various immunizations, blood tests, and exams, calculated from the patient data. There is little consensus between the health care provider and payer factions in this area; therefore, the schedule should be discussed with a physician. For example, the plan recommends a purified protein derivative as often as every 6 months for people at risk for tuberculosis, but makes no mention of prostate screening or mammography.

The smoking cessation section had a list of quitting methods and a test to

determine if the patient was ready to quit, but was incomplete at the time of the review.

The final portion was Personal or Decision Support. This provides a place to record medical history and a health calendar. The information can be used during health care visits, as well as by the patient to track treatment compliance or any other aspect. In addition, a fee-based service is provided that includes monitoring by a registered nurse and regular telephone calls to discuss the patient's health. The site states that the service may be covered by some health maintenance organizations or insurance plans, although no list was found.

Several support areas allow setting up e-mail reminders: some useful, some possibly not. Getting a reminder the day before an appointment might help jog the memory. Getting multiple e-mail messages each day to take medications would require an almost constant Internet connection and a slavish attachment to the computer. Even this reviewer does not spend enough time online during the day to make qid medication reminders timely. Unfortunately, none of the test e-mail reminders were received during the test period, despite receiving other e-mail from the site.

LifeMasters Online provides basic patient education, health management, and support. The pages were free of extraneous graphics and loaded quickly. Many other sources are available for the same information (a **www.yahoo.com** search found 278 site matches on asthma instruction). Various monitoring and graphing programs are also available for free (eg, **healthmonitor15.zip**) on the Internet. The added value of **LifeMasters Online** is integrating them and providing oversight. Two studies,[1,2] supported by **LifeMasters Online**, show health care services required by enrolled members were reduced in a program that included daily data entry and regular follow-up telephone calls. Neither study discussed the cost of the program. Whether this model proves to be an efficient part of the future health care delivery system remains to be seen. In the meantime, the site can be added to the list of useful patient resources.

REFERENCES

1. Heidenreich PA, Ruggerio CM, Massie BM. Effect of a home monitoring system on hospitalization and resource use for patients with heart failure. Am Heart J 1999;138(4 Pt 1):633–640.
2. Shah NB, Der E, Ruggerio CM, Heidenreich PA, Massie BM. Prevention of hospitalizations for heart failure with an interactive home monitoring program. Am Heart J 1998;135:373–378.

Steven B Nelson MS RRT
Overland Park, Kansas
Mayo Pulmonary Services
Rochester, Minnesota

Respiratory Product News
(reviewed April 10–18, 2000)

One should normally not judge a book, or any other medium, by its cover. However, in the case of **Respiratory Product News** (http://www.rpnmed.com) announcement letter and Web site, such a judgment would have been appropriate. The e-mail cover message from Scott Adams, Associate Publisher, sent to the American Association for Respiratory Care invited the reader to "vist [sic] the site," which contains "techonolgy [sic] features," and to leave ideas on how to "imporve [sic] the site." The featured editorial reviews a video that "segways [sic] into a demonstration of bronchoscopy." One wonders if a spelling checker should be at the top of the list of purchases for the fledgling company.

Respiratory Product News introduces itself with a blustery QuickTime movie in which the narrator declaims "Respiratory care is dynamic and dimensional **NOW,** so it must be experienced from electronic video net journal." The narrator also gives a short introduction to each of the video clips available on the site. It is quickly apparent that he has not been involved in health care for long, or has minimal medical training, from his creative reading of "thoracostomy, deheesis" and something called "media stentitis" as postoperative complications that can be avoided by using a new device. His veracity is easily questioned by about the third voice-over he delivers.

The introductory movie, which takes about 5 minutes to download with a normal 56 kilobyte dial-up connection, promises a "number of departments: sternum support, endoscopy, monitoring, ventilation, and other important respiratory topics." In reality, those were the only topics, along with a nebulizer, that had video clips available. While this reviewer admits to not venturing outside the pulmonary function lab for a number of years, I believe this is the first time that sternum support has topped any list of important respiratory topics.

Respiratory Product News offers industry news, video clips from several manufacturers, the ubiquitous list of links, and e-mail access to the editor. The whole site consists of about 4 pages, excluding the usual legal notices and disclaimers. Individual pages are not dated, denying an easy way to determine the currency of the news. It is a recent addition to the Internet: the domain was registered on December 19, 1999.

During the week ending April 13th, 2000, the industry news consisted of 8 items. Six were press releases, arguably related to respiratory care, gathered from one of the online financial news sources. The seventh was little more than an advertisement posing as a new Web site announcement for a pulmonary physicians' group. The last "news" item was provided by **Shaklee.com**. It explains how global warming is causing growing health concerns. A link to the Shaklee Web site offered to show how changing your activities can help to reduce atmospheric carbon dioxide. The reviewer did not check the program, but ponders if this means he should forego his daily exercise and

the accompanying increased production of CO_2 as a waste product. The dates of the original articles are not included with the synopsis, requiring the reader to open each page to determine how current it is. No archive of old news items is provided. There were 5 similar items added on April 14th, 2000.

Video clips can be effective training tools, and this site attempts to show that with selected parts taken from manufacturer-supplied information. The movies covering ventilators and ventilatory modes offer very elementary information, along with a sales pitch. Downloading a 7 megabyte file about a ventilator took about 15 minutes and resulted in the viewer learning little more than the 5 different modes of ventilation it offered. On the other hand, a short advertisement for a video-bronchoscope provided very good images obtained during bronchoscopy and pointed out interesting anatomical variants found in the patient being studied. **Respiratory Product News** takes credit for editing most of the clips to provide "interesting excerpts." The results did not seem particularly well done; the DHD Healthcare Thera-PEP clip ends mid-sentence. The listings on the video page provided no indication of file size or estimated download time. This is an unfortunate oversight, since several files were large and would take substantial time to download.

Link lists seem to be a requirement of all Web sites, and **Respiratory Product News** is no exception. They offer an extensive, somewhat organized list that spreads over many screens. When you click on a link, **Respiratory Product News** opens it within the **Respiratory Product News** frame rather than opening a new window to the linked site. This makes it impossible for the reader to automatically bookmark pages of interest. In addition, there are again numerous misspellings (eg, "Americain", "Terxas") and confusing, inconsistent use of upper case and lower case letters in uniform resource locators, which are essentially case-insensitive.

Online publishing differs from other traditional media in one important aspect: statement of ownership. Though each page at **Respiratory Product News** is copyrighted by Goldstein and Associates, there is no method of determining whether they are funded by vested interests or independent of external influence. More mainstream companies provide this information on their Web sites.

Another difficulty in reviewing online sources has to do with immediacy. Because of the rapid changes common at Web sites, any review must be considered in the time frame over which it was done. Unlike a book, electronic information can be, and usually is, altered after publication. This site was reviewed April 10–18, 2000. An off-line archive was made for reference at that time, but the site may have made substantial changes between its review date and the date of this publication.

Respiratory Product News gives the impression of a draft copy of the first few chapters of a book. It may be adequate for showing someone the potential scope, but it is far from a complete product. It presents random bits of information that are already available in a timely manner in weekly and monthly printed sources. There is no compelling reason to return to the site (commonly referred to in Internet terms as "magnetism") and therefore very little potential to draw sponsors or advertisers to provide funding and the ability to keep it up to date. It provides a good example of what may happen by rushing an idea to the public in the imaginary race to be first.

Steven B Nelson MS RRT
Overland Park, Kansas
Mayo Pulmonary Services
Rochester, Minnesota

Infusion/Blood Warmer. Futuremed introduces its new Animec Infusion Warmer (Models AM 124 & AM 125). According to the company, the Animec provides a convenient and safe way to protect patients from hypothermia and decreased oxygen availability. Futuremed describes the device as an electrically powered dry warmer that supplies heat to the infusion set tubing requiring only 2 to 3 minutes to warm up. Press materials say the warmer is designed for flow rates of 3-12 mL/min and that they can be used with standard hospital I.V. tubes of 4 mm (AM 124) and 5 mm (AM 125). Futuremed says the device is ideally suited for pediatrics, plastic surgery, recovery room, and other applications where low flow rates are applied. For more information from Futuremed, circle number 161 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

EEG and PSG Recording System. The Grass-Telefactor Product Group of Astro-Med Inc has introduced its latest advancement in ambulatory EEG and PSG recording. Called H_2O™ (Home to Office), this new product has been described by the company as a device ideal on its own for performing EEG and PSG recording in or out of the lab, and is perfect for the input to lab-based EEG/PSG consoles. Astro-Med says this device can acquire 32 channels plus oximetry and is designed to allow easy addition of redundant electrodes for backup in the unattended out-of-lab environment (all recorded information is stored continuously on an internal 6-gigabyte hard drive). For more information from the Grass-Telefactor Product Group of Astro-Med, circle number 162 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Surgical Glove. Maxxim Medical has recently released its SensiCare™ Synthetic Powder Free Surgical Gloves. According to company press materials, these new gloves are the first made with Isolex™, a polyisoprene polymer with the same molecular structure as natural latex rubber. Maxxim says company product tests found that the gloves outperformed all other synthetic surgical glove materials and that the glove's latex-like composition provides strength and elasticity without introducing the potential hazards of latex protein allergy. For more information from Maxxim Medical, circle number 163 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Online Ancillary Link System. Achieve Healthcare Information Systems introduces the Achieve PathLinks® Ancillary Link™ application. The company says this new system is designed to connect the care center to its various ancillary vendors. Achieve also says the system provides electronic access to vendors such as pharmacy, lab, and therapy and that it functions as an extension of the care center's information system—working with admissions, clinical, and financial applications. For more information from Achieve Healthcare Information Systems, circle number 164 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

www.rcjournal.com

the accompanying increased production of CO_2 as a waste product. The dates of the original articles are not included with the synopsis, requiring the reader to open each page to determine how current it is. No archive of old news items is provided. There were 5 similar items added on April 14th, 2000.

Video clips can be effective training tools, and this site attempts to show that with selected parts taken from manufacturer-supplied information. The movies covering ventilators and ventilatory modes offer very elementary information, along with a sales pitch. Downloading a 7 megabyte file about a ventilator took about 15 minutes and resulted in the viewer learning little more than the 5 different modes of ventilation it offered. On the other hand, a short advertisement for a video-bronchoscope provided very good images obtained during bronchoscopy and pointed out interesting anatomical variants found in the patient being studied. **Respiratory Product News** takes credit for editing most of the clips to provide "interesting excerpts." The results did not seem particularly well done; the DHD Healthcare Thera-PEP clip ends mid-sentence. The listings on the video page provided no indication of file size or estimated download time. This is an unfortunate oversight, since several files were large and would take substantial time to download.

Link lists seem to be a requirement of all Web sites, and **Respiratory Product News** is no exception. They offer an extensive, somewhat organized list that spreads over many screens. When you click on a link, **Respiratory Product News** opens it within the **Respiratory Product News** frame rather than opening a new window to the linked site. This makes it impossible for the reader to automatically bookmark pages of interest. In addition, there are again numerous misspellings (eg, "Americain", "Terxas") and confusing, inconsistent use of upper case and lower case letters in uniform resource locators, which are essentially case-insensitive.

Online publishing differs from other traditional media in one important aspect: statement of ownership. Though each page at **Respiratory Product News** is copyrighted by Goldstein and Associates, there is no method of determining whether they are funded by vested interests or independent of external influence. More mainstream companies provide this information on their Web sites.

Another difficulty in reviewing online sources has to do with immediacy. Because of the rapid changes common at Web sites, any review must be considered in the time frame over which it was done. Unlike a book, electronic information can be, and usually is, altered after publication. This site was reviewed April 10–18, 2000. An off-line archive was made for reference at that time, but the site may have made substantial changes between its review date and the date of this publication.

Respiratory Product News gives the impression of a draft copy of the first few chapters of a book. It may be adequate for showing someone the potential scope, but it is far from a complete product. It presents random bits of information that are already available in a timely manner in weekly and monthly printed sources. There is no compelling reason to return to the site (commonly referred to in Internet terms as "magnetism") and therefore very little potential to draw sponsors or advertisers to provide funding and the ability to keep it up to date. It provides a good example of what may happen by rushing an idea to the public in the imaginary race to be first.

Steven B Nelson MS RRT
Overland Park, Kansas
Mayo Pulmonary Services
Rochester, Minnesota

News releases about new products and services will be considered for publication in this section. There is no charge for these listings. Send descriptive release and glossy black and white photographs to RESPIRATORY CARE, New Products & Services Dept, 11030 Ables Lane, Dallas TX 75229-4593. The Reader Service Card can be found at the back of the Journal.

New Products & Services

Infusion/Blood Warmer. Futuremed introduces its new Animec Infusion Warmer (Models AM 124 & AM 125). According to the company, the Animec provides a convenient and safe way to protect patients from hypothermia and decreased oxygen availability. Futuremed describes the device as an electrically powered dry warmer that supplies heat to the infusion set tubing requiring only 2 to 3 minutes to warm up. Press materials say the warmer is designed for flow rates of 3-12 mL/min and that they can be used with standard hospital I.V. tubes of 4 mm (AM 124) and 5 mm (AM 125). Futuremed says the device is ideally suited for pediatrics, plastic surgery, recovery room, and other applications where low flow rates are applied. For more information from Futuremed, circle number 161 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

EEG and PSG Recording System. The Grass-Telefactor Product Group of Astro-Med Inc has introduced its latest advancement in ambulatory EEG and PSG recording. Called H_2O™ (Home to Office), this new product has been described by the company as a device ideal on its own for performing EEG and PSG recording in or out of the lab, and is perfect for the input to lab-based EEG/PSG consoles. Astro-Med says this device can acquire 32 channels plus oximetry and is designed to allow easy addition of redundant electrodes for backup in the unattended out-of-lab environment (all recorded information is stored continuously on an internal 6-gigabyte hard drive). For more information from the Grass-Telefactor Product Group of Astro-Med, circle number 162 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Surgical Glove. Maxxim Medical has recently released its SensiCare™ Synthetic Powder Free Surgical Gloves. According to company press materials, these new gloves are the first made with Isolex™, a polyisoprene polymer with the same molecular structure as natural latex rubber. Maxxim says company product tests found that the gloves outperformed all other synthetic surgical glove materials and that the glove's latex-like composition provides strength and elasticity without introducing the potential hazards of latex protein allergy. For more information from Maxxim Medical, circle number 163 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

Online Ancillary Link System. Achieve Healthcare Information Systems introduces the Achieve PathLinks® Ancillary Link™ application. The company says this new system is designed to connect the care center to its various ancillary vendors. Achieve also says the system provides electronic access to vendors such as pharmacy, lab, and therapy and that it functions as an extension of the care center's information system—working with admissions, clinical, and financial applications. For more information from Achieve Healthcare Information Systems, circle number 164 on the reader service card in this issue, or send your request electronically via "Advertisers Online" at http://www.aarc.org/buyers_guide/

www.rcjournal.com

Not-for-profit organizations are offered a free advertisement of up to eight lines to appear, on a space-available basis, in Calendar of Events in RESPIRATORY CARE. Ads for other meetings are priced at $5.50 per line and require an insertion order. Deadline is the 20th of the month two months preceding the month in which you wish the ad to run. Submit copy and insertion orders to Calendar of Events, RESPIRATORY CARE, 11030 Ables Lane, Dallas TX 75229-4593.

Calendar of Events

AARC & AFFILIATES

August 3—*Cleveland, Ohio*

The OSRC Critical Care Conference will be held at the Holiday Inn Rockside Road in Independence. This one-day conference will include presentations on sedation in the ICU, ARDS, weaning, transport of the critically ill, trauma in the ER, and inhalation injuries. An exhibit hall with more than 20 sponsors will be open, and six CRCEs are available. **Contact:** Nancy Johnson at (330) 929-7166 or **abbyru@aol.com**.

September 14-15–*Pittsburgh, Pennsylvania*

The PSRC Western Regional Pulmonary Conference will be held in conjunction with The Greater Pittsburgh Sleep Professionals at the Sheraton Station Square. The conference features education presentations on management, critical care, sleep diagnostics, pulmonary rehabilitation, the physician forum, and the GPSP sleep tract. **Contact:** Debbie Logan at (800) 545-4663, ext 112.

September 20-22—*Rochester, Minnesota*

The Minnesota Society for Respiratory Care host their 31st Annual Fall State Conference — "Too Hot to Handle." **Contact:** For more information, contact Laurie Tomaszewski at (651) 232-1922, Carolyn Dunow at **dunowc@fhpcare.com**, or Carl Mottram at **mottram.carl@mayo.edu**.

September 27–29—*Hot Springs, Arkansas*

The ASRC will hold its 29th Annual State Meeting and Education Seminar at the Austin Hotel and Hot Springs Convention Center. Speakers include AARC President Garry Kauffman, Vijay Deshpande, Dr Mark Heulitt, Dr Teofilo Lee-Choing, Harold Davis, Jeff Standridge, Lela Parish-Cooper, Shelley Dedman, James Lisenbey, John Campbell, and Theresa Gramlich. Topics will include ventilation in Y2K, home health, pulmonary medicine, asthma, and patient/practitioner rights. National vendors will present an exhibit of the latest technology. Contact John W Lindsey at (870) 541-7606 or **jlindsey@ahecpb.nams.edu**. Or visit **www.arksrc.org**.

October 6—*Cincinnati, Ohio*

The AARC is presenting three postgraduate courses immediately prior to the annual Congress. "Mechanical Ventilation" will include lung injury, managing airway obstruction, weaning, closed loop/dual control modes, and noninvasive ventilation. "Making Protocols Work in Your Institution" will cover rationale, legal aspects, and use in the ICU. "Developing and Enhancing Pulmonary Rehabilitation Services" addresses staffing, patient screening, reimbursement, and marketing. All courses are approved for continuing education credits, and attendance space is limited. **Contact:** For more information, see the Congress Program in the *AARC Times* July issue or call (972) 243-2272.

October 11-13–*Bossier City, Louisiana*

The LSRC's second annual Fall Convention will be held at the Isle of Capri Hotel and Casino with numerous national speakers and exhibitors. Ten CEUs will be available. **Contact:** For more information or booth reservations, call Shonda Houston at (318) 226-0555 or e-mail **sparta@lsumc.edu**.

November 10–12—*Ithaca, New York*

The NYSSRC and the ALACNY will host the Northeast Pulmonary Teaching Conference at Comell University. Faculty includes Jim Fink, Dean Hess, Bob Kacmarek, Neil MacIntyre, David Pierson, and more. Sessions examine acute and subacute respiratory care, RT management, NIPPV, pediatrics, and asthma. Exhibits, job fair, and family-friendly activities. **Contact:** For more information, call Patricia Kuhl at (315) 422-6142 or visit **www.nepulmonaryconf.com**.

Other Meetings

August 13-18—*Hobertus, Wisconsin*

The American Lung Association of Metropolitan Chicago is looking for a volunteer RT with a special interest in respiratory care for children. The RT will volunteer their time and provide structured asthma education one hour a day to children at the 18th annual CampACTION at YMCA Camp Minikani. The RT will also provide individual education in the cabins. Up to eight CEU credits are available. CampACTION is staffed 24 hours a day by physicians, nurses, an RT, and a pharmacist. **Contact:** If interested, call Evet Hexamer at (312) 243-2000, ext 260.

August 18-19–*Tampa, Florida*

The Alliance for Cardiovascular Professionals (ACP) and TechEd Consultants are sponsoring a spirometry course at the Saddlebrook Resort in conjunction with the ACP annual meeting. Tuition will be discounted for ACP and FSRC members. **Contact:** Call ACP at (540) 370-0102 or TechEd at (517) 676-7018.

September 26–29—*TechShop 2000*

If you are a polysomnographic technician seeking to enhance your professional skills, you need information about TechShop 2000. TechShop 2000 is a four-day introductory to intermediate level, hands-on, intensive training for polysomnographic technicians that covers patient preparation, set-up, scoring, troubleshooting, artifact recognition, and much more. Beginning Tuesday, Sept 26, and ending with Keynote Symposium Sept 29, TechShop 2000 is taught at one of the world's premier sleep disorders centers, Ohio Sleep Medicine Institute, under the medical direction of board-certified sleep specialist Dr Helmut Schmidt. For a detailed course outline, contact Crystal or Brian at (614) 792-7632 or e-mail **sleepohio@aol.com**.

Practical Spirometry Certification Course

Two-day hands-on NIOSH-approved course presented by Mayo Pulmonary Services: Sept 29–30 in Chicago IL; and Nov 9–10 in Rochester MN. NIOSH approval #57. Approved by AAOHN for 15.6 contact hours. **Contact:** For further details, call (800) 533-1653.

March 21–24, 2001—*Big Sky, Montana*

The American Lung Association of the Northern Rockies will host their 20th annual Big Sky Pulmonary & Critical Care Medicine Conference at the Big Sky Ski Resort. This multidisciplinary review and update for all health professionals interested in pulmonary and critical care medicine will offer 15 hours of CME credit. **Contact:** For more information, call (406) 442-6556 or e-mail **alamtwy@aol.com**.

American Association for Respiratory Care

MEMBERSHIP APPLICATION

Please read the eligibility requirements for each of the classifications in the right-hand column, then complete the applicable section. All information requested below must be provided, except where indicated as optional. See other side for more information and fee schedule. Please sign and date application on reverse side and type or print clearly. Processing of application takes approximately 15 days.

- ☐ Active
- Associate
  - ☐ Foreign
  - ☐ Physician
  - ☐ Industrial
- ☐ Special
- ☐ Student

Last Name _____

First Name _____

Social Security No. _____

Home Address _____

City _____

State _____ Zip __ __ __ __ __ — __ __ __ __

Phone No. (_____) _____

Primary Job Responsibility (check one only)

- ☐ Technical Director
- ☐ Assistant Technical Director
- ☐ Pulmonary Function Specialist
- ☐ Instructor/Educator
- ☐ Supervisor
- ☐ Staff Therapist
- ☐ Staff Technician
- ☐ Rehabilitation/Home Care
- ☐ Medical Director
- ☐ Sales
- ☐ Student
- ☐ Other, specify _____

Type of Business

- ☐ Hospital
- ☐ Skilled Nursing Facility
- ☐ DME/HME
- ☐ Home Health Agency
- ☐ Educational Institution
- ☐ Manufacturer or supplier
- ☐ Other, specify _____

Date of Birth (optional) _____ Sex (optional) _____

U.S. Citizen? ____ Yes ____ No

Have you ever been a member of the AARC? _____

If so, when? From _____ to _____

Preferred mailing address: ☐ Home ☐ Business

For office use only

FOR ACTIVE MEMBER

An individual is eligible if he/she lives in the U.S. or its territories or was an Active Member prior to moving outside its borders or territories, and meets ONE of the following criteria: (1) is legally credentialed as a respiratory care professional if employed in a state that mandates such, OR (2) is a graduate of an accredited educational program in respiratory care, OR (3) holds a credential issued by the NBRC. An individual who is an AARC Active Member in good standing on December 8, 1994, will continue as such provided his/her membership remains in good standing.

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE.

Place of Employment _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

Medical Director/Medical Sponsor _____

FOR ASSOCIATE OR SPECIAL MEMBER

Individuals who hold a position related to respiratory care but do not meet the requirements of Active Member shall be Associate Members. They have all the rights and benefits of the Association except to hold office, vote, or serve as chair of a standing committee. The following subclasses of Associate Membership are available: Foreign, Physician, and Industrial (individuals whose primary occupation is directly or indirectly devoted to the manufacture, sale, or distribution of respiratory care equipment or supplies). Special Members are those not working in a respiratory care-related field.

PLEASE USE THE ADDRESS OF THE LOCATION WHERE YOU PERFORM YOUR JOB, NOT THE CORPORATE HEADQUARTERS IF IT IS LOCATED ELSEWHERE.

Place of Employment _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

FOR STUDENT MEMBER

Individuals will be classified as Student Members if they meet all the requirements for Associate Membership and are enrolled in an educational program in respiratory care accredited by, or in the process of seeking accreditation from, an AARC-recognized agency.

SPECIAL NOTICE — Student Members do not receive Continuing Respiratory Care Education (CRCE) transcripts. Upon completion of your respiratory care education, continuing education credits may be pursued upon your reclassification to Active or Associate Member.

School/RC Program _____

Address _____

City _____

State _____ Zip __ __ __ __ __ - __ __ __ __

Phone No. (_____) _____

Length of program

- ☐ 1 year
- ☐ 2 years
- ☐ 4 years
- ☐ Other, specify _____

Expected Date of Graduation *(REQUIRED INFORMATION)*

Month _____ Year _____

American Association for Respiratory Care • 11030 Ables Lane • Dallas, TX 75229-4593 • [972] 243-2272 • Fax [972] 484-2720

American Association for Respiratory Care MEMBERSHIP APPLICATION

Demographic Questions

We request that you answer these questions in order to help us design services and programs to meet your needs.

Check the Highest Degree Earned

- ☐ High School
- ☐ RC Graduate Technician
- ☐ Associate Degree
- ☐ Bachelor's Degree
- ☐ Master's Degree
- ☐ Doctorate Degree

Number of Years in Respiratory Care

- ☐ 0-2 years
- ☐ 3-5 years
- ☐ 6-10 years
- ☐ 11-15 Years
- ☐ 16 years or more

Job Status

- ☐ Full Time
- ☐ Part Time

Credentials

- ☐ RRT
- ☐ CRT
- ☐ Physician
- ☐ CRNA
- ☐ RN
- ☐ LVN/LPN
- ☐ CPFT
- ☐ RPFT
- ☐ Perinatal/Pediatric

Salary

- ☐ Less than $10,000
- ☐ $10,001-$20,000
- ☐ $20,001-$30,000
- ☐ $30,001-$40,000
- ☐ $40,000 or more

PLEASE SIGN

I hereby apply for membership in the American Association for Respiratory Care and have enclosed my dues. If approved for membership in the AARC, I will abide by its bylaws and professional code of ethics. I authorize investigation of all statements contained herein and understand that misrepresentations or omissions of facts called for is couse for rejection or expulsion.

A yearly subscription to RESPIRATORY CARE journal and *AARC Times* magazine includes an allocation of $11.50 from my dues for each of these publications.

NOTE: Contributions or gifts to the AARC are not tax deductible as charitable contributions for income tax purposes. However, they may be tax deductible as ordinary and necessary business expenses subject to restrictions imposed as a result of association lobbying activities. The AARC estimates that the nondeductible portion of your dues — the portion which is allocable to lobbying — is 26%.

Signature _____

Date _____

Membership Fees

Payment must accompany your application to the AARC. Fees are for 12 months. (NOTE: Renewal fees are $75.00 Active, Associate-Industrial or Associate-Physician, or Special status; $90.00 for Associate-Foreign status; and $45.00 for Student status).

☐ Active	$ 87.50
☐ Associate (Industrial or Physician)	$ 87.50
☐ Associate (Foreign)	$102.50
☐ Special	$ 87.50
☐ Student	$ 45.00
TOTAL	$_____

Specialty Sections

Established to recognize the specialty areas of respiratory care, these sections publish a bi-monthly newsletter that focuses on issues of specific concern to that specialty. The sections also design the specialty programming at the national AARC meetings.

☐ Adult Acute Care Section	$15.00
☐ Education Section	$20.00
☐ Perinatal-Pediatric Section	$15.00
☐ Diagnostics Section	$15.00
☐ Continuing Care-Rehabilitation Section	$15.00
☐ Management Section	$20.00
☐ Transport Section	$15.00
☐ Home Care Section	$15.00
☐ Subacute Care Section	$15.00
TOTAL	$_____

GRAND TOTAL = Membership Fee plus optional sections $_____

- ☐ Total Amount Enclosed/Charged $_____
- ☐ Please charge my dues (see below)

To charge your dues, complete the following:

- ☐ MasterCard
- ☐ Visa

Card Number

— — — — — — — — — — — — — — — —

Card Expires _____/_____

Signature _____

Mail application and appropriate fees to:

American Association for Respiratory Care • 11030 Ables Lane • Dallas, TX 75229-4593 • (972) 243-2272 • Fax (972) 484-2720

MEDWATCH

THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

For VOLUNTARY reporting by health professionals of adverse events and product problems

Page ____ of ____

Form Approved: OMB No. 0910-0291 Expires: 4/30/96
See OMB statement on reverse

FOA Use Only (Resp Care)

Triage unit sequence #

A. Patient information

1. Patient identifier
In confidence

2. Age at time of event:
or
Date of birth:

3. Sex
☐ female
☐ male

4. Weight
____ lbs
or
____ kgs

B. Adverse event or product problem

1. ☐ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
☐ death ____ (mo/day/yr)
☐ life-threatening
☐ hospitalization – initial or prolonged
☐ disability
☐ congenital anomaly
☐ required intervention to prevent permanent impairment/damage
☐ other: ____

3. Date of event (mo/day/yr)

4. Date of this report (mo/day/yr)

5. Describe event or problem

6. Relevant tests/laboratory data, including dates

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1
#2

2. Dose, frequency & route used
#1
#2

3. Therapy dates (if unknown, give duration) from/to (or best estimate)
#1
#2

4. Diagnosis for use (indication)
#1
#2

5. Event abated after use stopped or dose reduced
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1
#2

7. Exp. date (if known)
#1
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # (for product problems only)
– –

10. Concomitant medical products and therapy dates (exclude treatment of event)

D. Suspect medical device

1. Brand name

2. Type of device

3. Manufacturer name & address

4. Operator of device
☐ health professional
☐ lay user/patient
☐ other: ____

5. Expiration date (mo/day/yr)

6.
model # ____
catalog # ____
serial # ____
lot # ____
other #

7. If implanted, give date (mo/day/yr)

8. If explanted, give date (mo/day/yr)

9. Device available for evaluation? (Do not send to FDA)
☐ yes ☐ no ☐ returned to manufacturer on ____ (mo/day/yr)

10. Concomitant medical products and therapy dates (exclude treatment of event)

E. Reporter (see confidentiality section on back)

1. Name & address

phone #

2. Health professional?
☐ yes ☐ no

3. Occupation

4. Also reported to
☐ manufacturer
☐ user facility
☐ distributor

5. If you do NOT want your identity disclosed to the manufacturer, place an " X " in this box. ☐

FDA

Mail to: MEDWATCH
5600 Fishers Lane
Rockville, MD 20852-9787

or FAX to:
1-800-FDA-0178

FDA Form 3500 1/96)

Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

ADVICE ABOUT VOLUNTARY REPORTING

Report experiences with:

- medications (drugs or biologics)
- medical devices (including in-vitro diagnostics)
- special nutritional products (dietary supplements, medical foods, infant formulas)
- other products regulated by FDA

Report SERIOUS adverse events. An event is serious when the patient outcome is:

- death
- life-threatening (real risk of dying)
- hospitalization (initial or prolonged)
- disability (significant, persistent or permanent)
- congenital anomaly
- required intervention to prevent permanent impairment or damage

Report even if:

- you're not certain the product caused the event
- you don't have all the details

Report product problems – quality, performance or safety concerns such as:

- suspected contamination
- questionable stability
- defective components
- poor packaging or labeling
- therapeutic failures

How to report:

- just fill in the sections that apply to your report
- use section C for all products except medical devices
- attach additional blank pages if needed
- use a separate form for each patient
- report either to FDA or the manufacturer (or both)

Important numbers:

- 1-800-FDA-0178 to FAX report
- 1-800-FDA-7737 to report by modem
- 1-800-FDA-1088 to report by phone or for more information
- 1-800-822-7967 for a VAERS form for vaccines

If your report involves a serious adverse event with a device and it occurred in a facility outside a doctor's office, that facility may be legally required to report to FDA and/or the manufacturer. Please notify the person in that facility who would handle such reporting.

Confidentiality: The patient's identity is held in strict confidence by FDA and protected to the fullest extent of the law. The reporter's identity, including the identity of a self-reporter, may be shared with the manufacturer unless requested otherwise. However, FDA will not disclose the reporter's identity in response to a request from the public, pursuant to the Freedom of Information Act.

The public reporting burden for this collection of information has been estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

DHHS Reports Clearance Office
Paperwork Reduction Project (0910-0291)
Hubert H. Humphrey Building, Room 531-H
200 Independence Avenue, S.W.
Washington, DC 20201

"An agency may not conduct or sponsor, and a peraon is not required to respond to, a collection of information unleaa it displays a currently valid OMB control number."

Please do NOT return this form to either of these addresses.

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service • Food and Drug Administration

FDA Form 3500-back

Please Use Address Provided Below – Just Fold In Thirds, Tape and Mail

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Rockville, MD 20857

Official Business
Penalty for Private Use $300

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES OR APO/FPO

BUSINESS REPLY MAIL
FIRST CLASS MAIL PERMIT NO. 946 ROCKVILLE, MD

POSTAGE WILL BE PAID BY FOOD AND DRUG ADMINISTRATION

MEDWATCH
The FDA Medical Products Reporting Program
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20852-9787

Manuscript Preparation Guide

RESPIRATORY CARE welcomes original manuscripts related to the science and technology of respiratory care and prepared according to the following instructions and the *Uniform Requirements for Manuscripts Submitted to Biomedical Journals* (available at http://www.acponline.org/journals/resource/unifreqr.htm). Manuscripts are blinded and reviewed by professionals who are experts in their fields. Authors are responsible for obtaining written permission to publish previously–published figures and tables from the original copyright holder. Accepted manuscripts are copyedited for clarity, concision, and consistency with RESPIRATORY CARE format. Before publication, authors receive page proofs for minor correction. Published papers are copyrighted by Daedalus Inc and may not be published elsewhere without permission. Editorial consultation is available at any stage of planning or writing for any submission; contact the Editorial Office.

Categories of Articles

Research Article: A report of an original investigation (a study). Must include Title Page, Abstract, Key Words, Background, Methods, Results, Discussion, Conclusions, and References. May also include Tables, Figures (if so, must include Figure Legends), Acknowledgments, and Appendices.

Review Article: A comprehensive, critical review of the literature and state-of-the-art summary of a topic that has been the subject of at least 40 published research articles. Must include: Title Page, Outline, Key Words, Introduction, Review of the Literature, Summary, and References. May also include: Tables, Figures (if so, must include Figure Legends), and Acknowledgments.

Overview: A critical review of a pertinent topic that has fewer than 40 published research articles. Same structure as Review Article.

Update: A report of subsequent developments in a topic that has been critically reviewed in RESPIRATORY CARE or elsewhere. Same structure as a Review Article.

Special Article: A pertinent paper not fitting one of the other categories. Consult with the Editor before writing or submitting such a paper.

Editorial: A paper addressing an issue in the practice or administration of respiratory care. It may present an opposing opinion, clarify a position, or bring a problem into focus.

Letter: A brief, signed communication responding to an item published in RESPIRATORY CARE or about other pertinent topics. Tables, Figures, and References may be included. The letter should be marked "For Publication."

Case Report: Report of an uncommon clinical case or a new or improved method of management or treatment. A case-managing physician must either be an author or furnish a letter approving the manuscript. Must include: Title Page, Abstract, Introduction, Case Summary, Discussion, and References. May also include: Tables, Figures (if so, must include Figure Legends), and Acknowledgments.

Point-of-View Paper: A paper expressing personal but substantiated opinions on a pertinent topic. Must include: Title Page, Text, and References. May also include Tables and Figures (if so, must include Figure Legends).

Drug Capsule: A miniature review paper about a drug or class of drugs that includes discussions of pharmacology, pharmacokinetics, or pharmacotherapy.

Graphics Corner: A brief case report discussing and illustrating waveforms for monitoring or diagnosis. Should include Questions, Answers, and Discussion sections.

Kittredge's Corner: A brief description of the operation of respiratory care equipment. Should include information from manufacturers and editorial comments and suggestions.

PFT Corner: A brief, instructive case report including pulmonary function testing, accompanied by a review of the relevant physiology and appropriate references to the literature.

Test Your Radiologic Skill: A brief, instructive case report involving pulmonary medicine radiography and including one or more radiographs. May involve imaging techniques other than conventional chest radiography.

Review of a Book, Film, Tape, or Software: A balanced, critical review of a recent release. RESPIRATORY CARE does not accept unsolicited book reviews; please contact the Editor if you have a suggestion for a book review.

Preparing the Manuscript

Print on one side of white 8.5 ×11 inch paper, with margins of at least 1 inch on all sides. Double-space the text and number the pages. Do *not* include author names, author institutional affiliations, or allusions to institutional affiliations anywhere except on the title page. On the Abstract page include the title but do not include author names. Begin each of the following on a new page: Title Page, Abstract, Text, Acknowledgments, References, each Table, each Figure, and each Appendix. Use standard English in the first person and active voice. Type all headings in initial-capital letters (eg, Background, Methods, Patients, Equipment, Statistical Analysis, Results, Discussion). Center the main section headings and place second-level headings on the left margin.

Abstract. Please ensure that the abstract does not contain any facts or conclusions that do not also appear in the body text. Limit the abstract to no more than 400 words.

Key Words. Research, Review, Overview, and Special Articles require Key Words. On the Abstract or Outline page, include a list of 6 to 10 key words or two-word phrases.

References. Assign reference numbers in the order that articles are cited in your manuscript. At the end of your manuscript, list the cited works in numerical order. Abbreviate journal names as in *Index Medicus*. List all authors. The following examples show RESPIRATORY CARE's style for references.

Article in a journal carrying pagination throughout the volume:

> Rau JL, Harwood RJ. Comparison of nebulizer delivery methods through a neonatal endotracheal tube: a bench study. Respir Care 1992;37(11):1233-1240.

Article in a publication that numbers each issue beginning with Page 1:

> Bunch D. Establishing a national database for home care. AARC Times 1991;15(Mar):61,62,64.

Corporate author journal article:

> American Association for Respiratory Care. Criteria for establishing units for chronic ventilator-dependent patients in hospitals. Respir Care 1988;33(11):1044-1046.

Article in journal supplement: (Journals differ in numbering and identifying supplements. Supply information sufficient to allow retrieval.)

> Reynolds HY. Idiopathic interstitial pulmonary fibrosis. Chest 1986; 89(3 Suppl):139S-143S.

Abstract in journal: (Abstracts citations are to be avoided, and those more than 3 years old should not be cited.)

> Stevens DP. Scavenging ribavirin from an oxygen hood to reduce environmental exposure (abstract). Respir Care 1990;35(11): 1087-1088.

Editorial in a journal:

> Enright P. Can we relax during spirometry? (editorial). Am Rev Respir Dis 1993;148(2):274.

Editorial with no author given:

> Negative-pressure ventilation for chronic obstructive pulmonary disease (editorial). Lancet 1992;340(8833):1440-1441.

Letter in journal:

> Aelony Y. Ethnic norms for pulmonary function tests (letter). Chest 1991;99(4):1051.

Corporate author book:

> American Medical Association Department of Drugs. AMA drug evaluations, 3rd ed. Littleton CO: Publishing Sciences Group; 1977.

Book: (For any book, specific pages should be cited whenever reference is made to specific statements or other content.)

> DeRemee RA. Clinical profiles of diffuse interstitial pulmonary disease. New York: Futura; 1990:76-85.

Chapter in book with editor(s):

> Pierce AK. Acute respiratory failure. In: Guenter CA, Welch MH, editors. Pulmonary medicine. Philadelphia: JB Lippincott; 1977:26-42.

Paper accepted but not yet published:

> Hess D. New therapies for asthma. Respir Care (year, in press).

Personal communication of unpublished data not yet accepted for publication: You must obtain written permission to cite unpublished data received via personal communication. Do not number such references, but instead make parenthetical reference in the body text of your manuscript. Example: "Recently, Jones found this treatment effective in 45 of 83 patients (Jones HI, University of the Cascades, 1999, personal communication)."

Tables. Tables should be consecutively numbered. Start each table on a separate page. Number and title the table and give each column a brief heading. Place explanations in footnotes, including all nonstandard abbreviations and symbols. Key the footnotes with the following symbols, superscripted, in the table body, and in the following order: *, †, ‡, §, ‖, ¶, **, ††. Do not use horizontal or vertical rules or borders. Do not submit tables as photographs, reduced in size, or on oversize paper.

Figures (illustrations). Figures include graphs, line drawings, photographs, and radiographs. Use only illustrations that clarify and augment the text. Number figures consecutively as Figure 1, Figure 2, etc. All the figures must be mentioned in the text. Every figure should have a legend (a title and/or description explaining the figure). Figure legends should appear as separate paragraphs at the end of the manuscript (after the References section), in the same computer file as the manuscript (not in a separate file, as with the tables and figures). Do not create scanned versions of figures borrowed from other publications; clear photocopies are preferable. To include figures previously published in other publications, you must obtain permission from the original copyright holder (see below). Figures must be of professional quality and a copy of the article from which the figure came should be available. If color is essential to the figure, consult the Editor for more information. In reports of animal experiments, use schematic drawings, not photographs. A letter of consent must accompany any photograph of an identifiable person. If possible, submit radiographs as prints and full-size copies of film.

Drugs. Precisely identify all drugs and chemicals used, giving generic names, doses, and methods of administration. Brand names may be given in parentheses after generic names.

Commercial Products. In the text, parenthetically identify commercial products only on first mention, giving the manufacturer's name, city, and state or country. Example: "We performed spirom-

etry (1085 System, Medical Graphics, Minneapolis, Minnesota)." Provide model numbers if available, and manufacturer's suggested price, if the study has cost implications.

Permissions: You must obtain written permission to use pictures of identifiable individuals or to name individuals in the Acknowledgments section. You must obtain written permission from the original copyright holder to use figures and tables from other publications. Copies of all applicable permissions must be on file at RESPIRATORY CARE before a manuscript goes to press. Copyright is most often held by the journal or book in which the figure or table originally appeared and applies to the creativity, style, and form in which the facts/data are presented to the reader; the facts themselves are not copyright-protectable. Therefore, if you were asking permission to reproduce a table or figure directly from a journal or book, or with minor adaptations, permission would be necessary. However, if you intend to extract some data from text or illustrations and present them in an entirely new form, permission would not be needed. Simply cite the source of the data using the following statement: "Figure adapted from data published in ..."

Ethics. When reporting experiments on human subjects, indicate that procedures were conducted in accordance with the ethical standards of the *World Medical Association Declaration of Helsinki* (see Respir Care 1997;42(6):635-636) or of the institution's committee on human experimentation. State that informed consent was obtained. Do not use patient's names, initials, or hospital numbers in text or illustrations. When reporting experiments on animals, indicate that the institution's policy, a national guideline, or a law on the care and use of laboratory animals was followed.

Statistics. Identify the statistical tests used in analyzing the data and give the prospectively determined level of significance in the Methods section. Report actual p values in the Results section. Cite only textbook and published article references to support choices of tests. As with commercial products (see above), parenthetically identify any general-use or commercial computer programs used.

Units of Measurement. Express measurements of length, height, weight, and volume in metric units appropriately abbreviated; temperatures in degrees Celsius; and blood pressures in millimeters of mercury (mm Hg). Report hematologic and clinical-chemistry measurements in conventional metric and in SI (*Système Internationale*) units (units and conversion factors listed at Respir Care 1997;42(6):640). Show gas pressures (including blood gas tensions) in millimeters of mercury (mm Hg).

Conflict of Interest. On the cover page, authors must disclose any liaison or financial arrangement they have with a manufacturer or distributor whose product is addressed in the manuscript or with the manufacturer or distributor of a competing product. Such arrangements do not disqualify a paper from consideration and are not disclosed to reviewers. Reviewers are screened for possible conflict of interest.

Abbreviations and Symbols. Use standard abbreviations and symbols, listed at Respir Care 1997;42(6):637-642. Do not create new abbreviations. Do not use abbreviations in the title, in section headings, and do not use unusual abbreviations in the abstract. Use an abbreviation only if the term occurs 4 or more times in the paper. Define all abbreviations (ie, write out the full term on first mention, followed by the abbreviation in parentheses) and thereafter use only the abbreviation. Standard units of measurement and scientific terms can be abbreviated without explanation (eg, L/min, mm Hg, pH, O_2). Please use the following forms: cm H_2O (not cmH_2O), f (not bpm), L (not l), L/min (not LPM, l/min, or lpm), mL (not 'ml), mm Hg (not mmHg), pH (not Ph or PH), $p > 0.001$ (not $p>0.001$), s (not sec), S_{pO_2} (arterial oxygen saturation measured via pulse-oximetry).

Prior and Duplicate Publication. In general, do not submit work that has been published or accepted elsewhere, though in special instances the Editor may consider such material if the original publisher grants permission. Please consult the Editor before submitting such work.

Authorship. All persons listed as authors should have participated in the reported work and in the shaping of the manuscript, all must have proofread the submitted manuscript, and all should be able to publicly discuss and defend the paper's content. A paper of corporate authorship must specify the key persons responsible for the article. Attribution of authorship is not based solely on solicitation of funding, collection or analysis of data, provision of advice, or similar services. Persons who provide such ancillary services may be recognized in an Acknowledgments section.

Reviewers: Please supply the names, credentials, affiliations, addresses, and phone/fax numbers of 3 professionals whom you consider expert on the topic of your paper. Your manuscript may be sent to one or more of them for blind peer review.

Submitting the Manuscript

Submit three printed copies and one (3.5-inch) computer diskette. The printed copies should each include photocopies of all of the Figures, Tables, and Appendixes. On the diskette, the manuscript should be in one file and the tables in a separate file. If soft copies of the figures are available, they should also be in a separate file. *However, do not create scanned versions of figures borrowed from other publications; clear photocopies are preferable.* Include the completed Cover Letter and Checklist (see next page) and permission letters. Mail to RESPIRATORY CARE, 600 Ninth Avenue, Suite 702, Seattle WA 98104. Do not fax manuscripts. Receipt will be acknowledged.

RESPIRATORY CARE
Editorial Office:

600 Ninth Avenue, Suite 702
Seattle WA 98104

(206) 223-0558 (voice)
(206) 223-0563 (fax)
rcjournal@aarc.org
rcjkk@oz.net

Cover Letter & Checklist

A copy of this completed form must accompany all manuscripts submitted for publication.

Title of Paper: _____

Publication Category: _____

Corresponding Author: _____ Phone: _____ FAX: _____

Mailing Address: _____

Reprints: ❑ Yes ❑ No E-mail Address: _____

"We, the undersigned, have all participated in the work reported, proofread the accompanying manuscript, and approve its submission for publication." Please print and include credentials, title, institution, academic appointments, city and state. If more than 4 authors, please use another copy of this form.*

*First Author: _____

Author Signature/Date _____

*Second Author: _____

Author Signature/Date _____

*Third Author: _____

Author Signature/Date _____

*Fourth Author: _____

Author Signature/Date _____

Has this research been presented in any public forum? ❑ Yes ❑ No

If yes, where, when and by whom? _____

Has this research received any awards? ❑ Yes ❑ No

If yes, please describe. _____

Has this research received any grants or other support, financial or material? ❑ Yes ❑ No

If yes, please describe. _____

Do any of the authors of this manuscript have a financial interest in (or a commercial or consulting relationship to) any of the products or manufacturers mentioned in this paper or any competing products or manufacturers? ❑ Yes ❑ No

If yes, please describe. _____

CHECKLIST

- ❑ Have you enclosed a copy of the manuscript on diskette?
- ❑ Is double-spacing used throughout entire manuscript?
- ❑ Are all pages numbered in upper-right corners?
- ❑ Are all references, figures, and tables cited in the text?
- ❑ Has the accuracy of the references been checked, and are they correctly formatted?
- ❑ Have SI values been provided?
- ❑ Has all arithmetic been checked?
- ❑ Have generic names of drugs been provided?
- ❑ Have necessary written permissions been provided?
- ❑ Have authors' names been omitted from text and figure labels?
- ❑ Have copies of 'in press' references been provided?
- ❑ Has the manuscript been proofread by all the authors?
- ❑ Have the manufacturers and their locations been provided for all devices and equipment used?

Notices

Notices of competitions, scholarships, fellowships, examination dates, new educational programs, and the like will be listed here free of charge. Items for the Notices section must reach the Journal 60 days before the desired month of publication (January 1 for the March issue, February 1 for the April issue, etc). Include all pertinent information and mail notices to RESPIRATORY CARE Notices Dept, 11030 Ables Lane, Dallas TX 75229-4593.

Scheduled Professor's Rounds 2000

Pediatric Ventilation: Kids Are Different—Mark Heulitt MD; Host, Richard Branson RRT—Video July 25; Audio August 15

What Matters in Respiratory Monitoring: What Goes and What Stays—Dean Hess PhD RRT FAARC; Host, Richard Branson RRT—Video August 22; Audio September 26

Managing Asthma: An Update—Patti Joyner RRT CCM; Host, Mari Jones MSN RN RRT—Video September 19; Audio October 17

Routine Pulmonary Function Testing: Doing It Right—Carl D Mottram RRT RPFT; Host, David Pierson MD—Video November 7; Audio December 5

RESPIRATORY CARE Journal has been selected by the Literature Selection Technical Review Committee of the National Library of Medicine to be indexed and included in *Index Medicus* and MEDLINE, which is available online in the U.S. and throughout the world. All articles in the Journal beginning with the January 2000 issue will be included.

Helpful Web Sites

American Association for Respiratory Care
http://www.aarc.org
- —Current job listings
- —American Respiratory Care Foundation fellowships, grants, & awards
- —Clinical Practice Guidelines

National Board for Respiratory Care
http://www.nbrc.org

RESPIRATORY CARE online
http://www.rcjournal.com
- —Subject and Author Indexes
- —Contact the editorial staff
- —OPEN FORUM; submit your abstract online

Asthma Management Model System
http://www.nhlbi.nih.gov

Keys to Professional Excellence
http://www.aarc.org/keys/

The National Board for Respiratory Care—Examination Dates and Fees for 2000

Examination	Examination Fees
CRT	$190 (new applicant) $150 (reapplicant)
Perinatal/Pediatric	$250 (new applicant) $220 (reapplicant)
CPFT	$200 (new applicant) $170 (reapplicant)
RPFT	$250 (new applicant) $170 (reapplicant)
RRT (Written & CSE)	$190 (new - written only) $200 (new - CSE only) $390 (new - both)

For information about other services or fees, write to the National Board for Respiratory Care, 8310 Nieman Road, Lenexa KS 66214, or call (913) 599-4200, FAX (913) 541-0156, or e-mail: nbrc-info@nbrc.org

Authors in This Issue

Bidani, Akhil 817
Brooks, Lee J 888
Campbell, Sammy C 864
Cockcroft, Donald W 886
Colice, Gene L 846
Corkery, Kevin 831
Duarte, Alexander G 817
Fink, James B 824, 874
Fuloria, Mamta 868
Manthous, Constantine A 815
Medoff, Benjamin D 887
Momii, Keith 817
Nelson, Steven B 890, 891
O'Riordan, Thomas G 836
Rau, Joseph L 824, 854
Rubin, Bruce K 868
Spahn, Joseph D 886
Witek, Theodore J Jr 826

Advertisers in This Issue

To advertise in RESPIRATORY CARE, contact Tim Goldsbury, 20 Tradewinds Circle, Tequesta FL 33469 at (561) 745-6793, Fax (561) 745-6795, e-mail: goldsbury@aarc.org, for rates and media kits. For recruitment/ classified advertising contact Beth Binkley, Marketing Assistant for RESPIRATORY CARE, at (972) 243-2272, Fax (972) 484-6010. Dale Griffiths is the Marketing Director for RESPIRATORY CARE.

Company	Product	Circle #	Phone	Page #
Bio-logic Systems	Digital Polysomnography	125	800-323-8326	794
DEY	Low Volume Surfactant	138	SEE AD	C2, 793
DEY	Sterile Solutions	150	800-755-5560	813
DHD Healthcare	EZ-PAP	137	800-847-8000	C4
Hans Rudolph, Inc.	Breathing Lung Model	131	800-456-6695	807
Hospital Hub.com	Recruitment	124	888-562-4357	803
Ingmar Medical, Inc.	Lung Simulator	104	800-585-9910	803
Monaghan Medical Corp	AeroChamber Plus	133	800-833-9653	796
Monaghan Medical Corp	AeroEclipse	127	800-833-9653	807
Newport Medical	Ventilator	118	800-451-3111	798
Siemens Medical Systems	Clinical Management Program	112	800-333-8646	C3
Texas Health Resources	Recruitment	140	SEE AD	811

COPYRIGHT INFORMATION. RESPIRATORY CARE is copyrighted by Daedalus Enterprises Inc. Reproduction in whole or in part without the express written permission of Daedalus Enterprises Inc is prohibited. Permission to photocopy a single article in this Journal for noncommercial purposes of scientific or educational advancement is granted. Permission for multiple photocopies and copies for commercial purposes must be requested in writing, via e-mail (rcjournal@aarc.org), or telephone and approved by RESPIRATORY CARE. Anyone may, without permission, quote up to 500 words of material in this journal provided the quotation is for noncommercial use and RESPIRATORY CARE is credited. Longer quotation requires written approval by the author and publisher. Single reprints are available only from the authors. Reprints for commercial use may be purchased from Daedalus Enterprises Inc. For more information and prices call (972) 243-2272.

DISCLAIMER. The opinions expressed in any article or editorial are those of the author and do not necessarily reflect the views of the Editors, the American Association for Respiratory Care (AARC), or Daedalus Enterprises Inc. Neither are the Editors, the AARC, or the Publisher responsible for the consequences of the clinical applications or use of any methods or devices described in any article or advertisement.

SUBSCRIPTION RATES. Individual subscription rates are $75 per year (12 issues), $145 for 2 years, and $215 for 3 years in the US and Puerto Rico. Rates are $90 per year, $175 for 2 years, and $260 for 3 years in all other countries (add $94 per year for air mail). Single copies when available cost $10; add $9 for air mail postage to overseas countries. Checks should be made payable to RESPIRATORY CARE and sent to the subscription office at 11030 Ables Lane, Dallas TX 75229-4593, or call (972) 243-2272.

SUBSCRIPTION RATES FOR ASSOCIATIONS. Basic annual subscriptions are offered to members of associations according to their membership enrollment: 101-500 members = $13.50/year; 501-1,500 = $13/year; 1,500-10,000 = $12.50/year; more than 10,000 = $11.50/year. Individual subscriptions ar available at these rates: $75/year (12 issues in the United States or Puerto Rico; $90/year in other countries. For information, contact Ray Masferrer at (972) 243-2272.

CHANGE OF ADDRESS. Notify the AARC at (972) 243-2272 as soon as possible of any change in address. Note the subscription number (from the mailing label) and your name, old address, and new address. Allow 6 weeks for the change. To avoid charges for replacement copies of missed issues, requests must be made within 60 days in the US and 90 days in other countries.

MANUSCRIPTS. The Journal publishes clinical studies, method/device evaluations, reviews, and other materials related to cardiopulmonary medicine and research. Manuscripts may be submitted to the Editorial Office, RESPIRATORY CARE, 600 Ninth Avenue, Suite 702, Seattle WA 98104. Instructions for authors are printed in every issue. An expanded version of the Instructions is available from the editorial office.

SIEMENS

Subscription

RESPIRATORY CARE
Subscription Form

RESPIRATORY CARE is the most highly regarded peer-reviewed scientific publication for the Clinician participating in the evaluation and care of patients with cardiopulmonary problems. **Please print; Incomplete forms will not be processed. For faster service, fax to (972)484-2720**

DON'T MISS A SINGLE ISSUE!

	U.S. Subscriptions	Subscriptions Outside U.S.
1 YR (12 Issues)	☐ $75	☐ $90
2 YRS (24 Issues)	☐ $145	☐ $175
3 YRS (36 Issues)	☐ $215	☐ $260

Enclosed is a check in the amount of $ _____

Charge to my:
☐ Mastercard
☐ Visa
☐ Bill Me

Signature | Expiration Date | Credit Card Number

Name | Title

Facility Name

Address

City | State | Zip Code | Country

Telephone | Fax

RESPIRATORY CARE

FREE
Product Information

Receive FREE information on the products and services mentioned in this issue, by circling the corresponding advertiser's number. Fill in your name and address and mail this postage-paid card. Information will be sent directly to you from the manufacturer. **Incomplete forms will not be processed.**

MAIL TODAY
OR FOR FASTER SERVICE
FAX TO
(609) 786-4415

For AARC membership information, circle 101. For Respiratory Care subscription information, circle 102.

101	102	103	104	105	106	107	108	109	110	111	112	113	114	115	116	117	118
119	120	121	122	123	124	125	126	127	128	129	130	131	132	133	134	135	136
137	138	139	140	141	142	143	144	145	146	147	148	149	150	151	152	153	154
155	156	157	158	159	160	161	162	163	164	165	166	167	168	169	170	171	172
173	174	175	176	177	178	179	180	181	182	183	184	185	186	187	188	189	190
191	192	193	194	195	196	197	198	199	200								

Please circle no more than 15 items.

Name | Title

Facility Name

Address

City | State | Zip Code | Country

Telephone | Fax

July 2000 Expires 10/15/00

RESPIRATORY CARE

I TYPE OF INSTITUTION OR PRACTICE
1 ☐ Hospital
2 ☐ Skilled Nursing Facility
3 ☐ Subacute Care Facility
4 ☐ Home Care Practice
5 ☐ School
6 ☐ Distributor

II DEPARTMENT
A ☐ Respiratory Care
B ☐ Cardiopulmonary
C ☐ Subacute Care
D ☐ Home Care

III SPECIALTY
1 ☐ Clinician
2 ☐ Perinatal/ Pediatrics
3 ☐ Critical Care
4 ☐ Research
5 ☐ Subacute Care
6 ☐ Diagnostics/ Pulmonary Function
7 ☐ Management
8 ☐ Home Care
9 ☐ Rehabilitation
10 ☐ Education

IV POSITION
A ☐ Department Head
B ☐ Chief Therapist
C ☐ Supervisor
D ☐ Staff Therapist/ Technician
E ☐ Medical Director
F ☐ Educator/Instructor
G ☐ Sales
H ☐ Other (please specify)

V ARE YOU AN AARC MEMBER?
1 ☐ Yes 2 ☐ No

© Siemens Medical Systems, Inc., Electromedical Systems Division, 1999

Management Program.™
related costs, and

300A — the most
e its full potential with

o shift your ventilator
ovement plans tailored
protocols and clinical
tical pathways, you
When you continuously
Ultimately, you improve

ebsite at

on product info card

Siemens Racing

sor of the #22 Pontiac Grand
NASCAR Winston Cup Series.

878-907-6300

Authors in This Issue

Bidani, Akhil 817
Brooks, Lee J 888
Campbell, Sammy C 864
Cockcroft, Donald W 886
Colice, Gene L 846
Corkery, Kevin 831
Duarte, Alexander G 817
Fink, James B 824, 874
Fuloria, Mamta 868
Manthous, Constantine A 815
Medoff, Benjamin D 887
Momii, Keith 817
Nelson, Steven B 890, 891
O'Riordan, Thomas G 836
Rau, Joseph L 824, 854
Rubin, Bruce K 868
Spahn, Joseph D 886
Witek, Theodore J Jr 826

Adverti in This Is

Company

Bio-logic Systems
DEY
DEY
DHD Healthcare
Hans Rudolph, Inc.
Hospital Hub.com
Ingmar Medical, Inc.
Monaghan Medical C
Monaghan Medical C
Newport Medical
Siemens Medical Syst
Texas Health Resourc

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 2480 Dallas,TX
POSTAGE WILL BE PAID BY ADDRESSEE

AARC Subscriptions
ATTN: Beth Binkley
PO BOX 29686
Dallas TX 75229-9691

NO POSTAGE NECESSARY IF MAILED IN THE UNITED STATES

BUSINESS REPLY MAIL
FIRST-CLASS MAIL PERMIT NO. 881 Riverton, NJ
POSTAGE WILL BE PAID BY ADDRESSEE

AARC Publications
PO BOX 11605
Riverton NJ 08076-7205

COPYRIGHT INFORM
Daedalus Enterprises Inc. written permission of Da photocopy a single artic scientific or educational photocopies and copies f ing, via e-mail (rcjournal RATORY CARE. Anyone material in this journal pı RESPIRATORY CARE i: proval by the author and authors. Reprints for con terprises Inc. For more ir

DISCLAIMER. The opir of the author and do no American Association f prises Inc. Neither are th for the consequences of tl vices described in any ar

SUBSCRIPTION RATE (12 issues), $145 for 2 Rico. Rates are $90 per y countries (add $94 per y $10; add $9 for air mail

SIEMENS

Master the machine for championship performance.

© Siemens Medical Systems, Inc., Electromedical Systems Division, 1999

The tools.
The skills.
The results.

Accelerate your skills to a new level with the Siemens Clinical Management Program.™ You'll reduce ventilator length of stay by at least 5%, minimize related costs, and improve overall performance. Guaranteed.

You're already ahead of the pack with the Servo Ventilator 300A — the most comprehensive ventilator platform available today. Now realize its full potential with this unique program.

We begin by benchmarking your current ventilator practices. To shift your ventilator use into high gear, we help you develop detailed process improvement plans tailored to your specific goals. When you implement disease-specific protocols and clinical interventions, you minimize ICU days. When you know the critical pathways, you may lessen the need for sedation and diagnostic intervention. When you continuously monitor the processes, you start to witness the cost savings. Ultimately, you improve patient outcomes, and get the most from your machine.

It's the championship performance you demand.

Speed success. Call Siemens at (800) 333-8646 or visit our website at www.sms.siemens.com/emdus

Circle 112 on product info card

Siemens Clinical Management Program | See it all come together.

AARC ZENITH AWARD 1999

Siemens Racing

Siemens is a proud sponsor of the #22 Pontiac Grand Prix in the NASCAR Winston Cup Series.

Siemens Medical Systems, Inc., Electromedical Systems Division 16 Electronics Avenue Danvers, MA 01923 Tel. 978-907-6300

Need more aggressive lung expansion therapy? Now, your choice is EZ.

New EZ-PAP.™ The EASY option for atelectasis.

When incentive spirometry alone won't open patients' airways, expand your options with new EZ-PAP. It makes providing positive airway pressure positively easy. Simply connect to a flow meter (wall air or O_2 for enhanced FiO_2), adjust to 5-15 lpm, and instruct the patient to breathe diaphragmatically through the mouthpiece or mask. No equipment to roll around. No labor-intensive CPT. No extensive training. Just a few minutes of therapy, once an hour — not for hours at a time.

EZ-PAP features a pressure port for connection to a gauge (recommended for initial use with each patient), and standard 22-mm OD fitting to accommodate a mouthpiece or 3 mask options. For more information, call DHD Healthcare toll-free today: **1-800-847-8000.**

DHD Healthcare

Innovations for respiratory care

One Madison Street, Wampsville, NY 13163 USA
(800) 847-8000 (315) 363-2330 FAX: (315) 363-5694
www.dhd.com

EZ-PAP is a trademark of DHD Healthcare Corporation
© 2000 DHD Healthcare Corporation

Circle 137 on product info card